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Errata

In the January number the title of Dr. L. N. Katz in the list of contributors and on the first page of his article should read: "*Professorial* Lecturer of Physiology," etc.

The last sentence on page 248 of Dr. Theron G. Randolph's paper should read: "The continuation of even small amounts of corn starch or corn sugar (glucose, dextrose and *Cerelose*) in an elimination diet will perpetuate symptoms in a patient highly sensitive to corn."

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FROM THE CLEVELAND CLINIC, CLEVELAND, OHIO

THE MEDICAL CLINICS
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NATIONWIDE NUMBER

SYMPOSIUM ON DISEASES OF THE DIGESTIVE SYSTEM

CLINICAL CONFERENCE ON VAGOTOMY

DWIGHT L. WILBUR, M.D., F.A.C.P., GARNETT CHENEY, M.D., AND CARLETON MATHEWSON, M.D., F.A.C.S.

DR. DWIGHT L. WILBUR: This morning we will debate vagotomy as a method of treatment for peptic ulcer. This is a subject about which there has been a great deal of discussion among members of the medical profession.

Dr. Cheney will comment upon the physiological basis for the clinical use of vagotomy in the treatment of ulcer, and some of the effects of vagotomy on the stomach. Doctor Mathewson has kindly consented to discuss vagotomy as it appears to the surgeon. And I shall say a few words about the clinical aspects of vagotomy. At the conclusion of our remarks we shall gladly try to answer any questions from the audience.

PHYSIOLOGIC ASPECTS

DR. GARNETT CHENEY: As regards the basic physiology of vagotomy, I would like to say first and with emphasis that the aim of vagotomy is to produce achlorhydria. This is the sole aim of a surgical operation which is known to be somewhat difficult and at times complicated, and for the following reason: If there is anything that most authorities agree on, in regard to the genesis or the causative factors of peptic ulcer, it is that peptic ulcer is due to peptic digestion of the gastric, duodenal or jejunal mucosa. Most authorities have come to this conclusion, and I think we can accept it as one of the few things on which gastroenterologists, internists and physiologists do agree. You must have acid secretion in the stomach—hydrochloric acid—and you

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must have pepsin. You must have acid before you get digestion of the gastric mucosa, or, following an operative procedure, the jejunal mucosa.

Now if we start from there, what has been accomplished in this respect in the past and why might vagotomy be any better? Well, if we think back, practically all our medical and surgical treatments have been directed primarily and fundamentally at producing either achlorhydria or very low gastric acidity in order to prevent this peptic digestion. We go back to the time of Sippy. I won't go into his work in detail, but the frequent feedings of milk kept acidity down, soluble alkalies kept it down, and as we come to the present time the various alkalies we use now, while not soluble, do produce more or less constant anacidity in the stomach. There has been a host of other procedures used. Now we have enterogasterone, a hormone which depresses gastric acidity. Practically all these medical treatments have been directed at reducing or eliminating free acidity in the stomach so as to eliminate peptic digestion. Surgical procedures such as gastroenterostomy, partial gastrectomy and pyloroplasty have had the same aim.

Coming now to the subject of vagotomy we might inquire of the role of the vagus nerves in the control of the stomach, and ask why their interruption or the carrying out a gastric neurectomy is important in this respect? The vagus nerves control the psychic secretion of acid by the stomach. They control the degree of peristalsis of the stomach, and more or less carry the protoplasmic sensory patterns concerned with gastric pain or pain reaching our cerebrum to make us conscious of pain in the stomach. The operating procedure had been carried out in dogs a good many years ago. In human subjects a rather large series was reported in 1938 by Winkelstein and some confreres in which vagotomy was performed in addition to partial gastric resection. The results of that combined procedure, going back almost ten years now, were that while most of the patients developed achlorhydria, about one-fourth of them did not develop it. Doctor Nelson Howard at Stanford carried out the same procedure eighteen years ago in the dog, and it produced low or absent acidity and marked gastric retention.

In respect to the group of patients which has had vagotomy alone, particularly as a follow-up of Dragstedt's work, there have been numerous, almost weekly, reports. Section of the vagus in the human, either above or below the diaphragm, if it is done satisfactorily, produces a striking relief of pain of ulcer. There is no question about that. The relief from pain after recovery from the operation is 100 per cent. Doubtless Doctor Mathewson will mention that point. The operation also produces a rather severe diarrhea in about four-fifths of the patients. The diarrhea may be slight and transitory or persistent and troublesome; and I don't know that we can tell beforehand which patient will have severe diarrhea. Another result in man, as well as

in dogs, is gastric retention. There is interference with normal motility and a certain amount of gastric atony results. It may on occasion be asymptomatic, but at other times vomiting is persistent and the condition proves very troublesome. In some patients the retention clears up in a few days or weeks, in others it persists for long periods of time.

As regards the type of the operation—whether one operates from above the diaphragm or below—all I need mention is that obviously the abdominal route is to be chosen, for with it the ulcer can be well observed. This is important in determining the exact condition of the stomach and duodenum.

The aims of this operation, as you know, are the relief of pain and the production of an achlorhydria to prevent the recurrence of ulcer. In dogs, although these aims are accomplished temporarily, gastric acidity usually returns, gastric motility returns and diarrhea ceases if the dogs are followed one or two years. Whether this experience will be repeated in humans, we do not yet know.

I should also mention the purpose of the postoperative insulin test, the effect of which is comparable to the psychogenic stimulation of acid juice when a patient thinks of a big beefsteak. If the operation has been successful, production of hypoglycemia by this method will not result in increase of the gastric secretion, which is proof that psychogenic stimulation of the gastric secretion, the only stimulation which should be abolished by the vagotomy operation, does not occur. We must remember that, even though the vagus is severed, gastric secretion may occur locally in a normal physiological manner and produce acid in the stomach.

CLINICAL ASPECTS

DR. WILBUR: I think you can see from Doctor Cheney's discussion of the physiological aspects of vagotomy that a great many problems may arise in the use of such a procedure in the surgical treatment of a disease which is as difficult to manage and as chronic as is peptic ulcer.

In the first place there are certain characteristics about peptic ulcer which we must remember. Such ulcers have two great tendencies, one of which is to heal and the other of which is to recur. It is these two tendencies which make it so difficult for us to evaluate the effects of treatment, because under normal circumstances ulcers tend to heal and they tend subsequently to recur. These facts are well known to those of you who have an ulcer. A second important fact to keep in mind is that in the opinion of a considerable number of experienced clinicians an ulcer is important only in that it may produce complications. By this I mean that the ulcer-bearing type of individual has a certain, psychic set-up which may predispose him to development of an ulcer. The ulcer itself may be simply one expression of a funda-

mental disturbance in such an individual. Therefore, to pay all of our attention in treatment to the ulcer alone and to forget to treat the individual who carries it may not give a good therapeutic result. An ulcer may be important then only in that it may penetrate, that it may bleed, or that it may lead to obstruction of the pylorus.

Now, keeping in mind the tendency of ulcers to heal and to recur, and considering the fact that there may be a good deal more to an ulcer-bearing patient than his ulcer, one can approach consideration of the problem of vagotomy and the results of it a little bit more soundly. As you all know, when vagotomy was first revitalized by Dragstedt some four years ago, the initial results which were reported by him and subsequently by Moore of the Massachusetts General Hospital and by Grimson of Duke University were extremely good. Several conservative gastroenterologists have spoken highly of the effectiveness of vagotomy for ulcer. Since that time a variety of opinions has been expressed and for some observers there has been a lessening in the initial enthusiasm for vagotomy for reasons, some of which I will try to bring out, and others of which I am sure Doctor Mathewson will discuss.

Priestley has very well pointed out that there is great difficulty in evaluating vagotomy clinically. The difficulties are: first, that one must have a uniform type of case, second, that one must be sure that the vagotomy is complete, and third, vagotomy alone must have been done in order to evaluate the results. As each year has passed more and more patients for whom vagotomy has been done have had a secondary operation performed on the stomach at the same time. In a considerable number of instances the vagotomy has not been complete, and there has not always been uniformity of the cases. Consequently the results of vagotomy are very difficult to determine in a series of any size, and in series from type different clinics comparison is even more difficult. Such comparative data are essential, however, before we can evaluate the usefulness of this procedure.

I think one can say very briefly that, in so far as *gastric* ulcer is concerned, vagotomy is not a suitable procedure for the following reasons. In the first place, there is always the problem as to whether or not an ulcerating lesion of the stomach is benign or malignant. To perform a vagotomy only and fail to remove the gastric lesion is not a good surgical procedure. I have observed one patient with an apparent benign ulcer of the stomach on whom a transthoracic vagotomy was performed and who a year later had metastasis from his gastric carcinoma. That experience is not an exceptional one.

The second point is that there have been a number of cases noted in which following vagotomy and excision of the gastric ulcer the gastric ulcer has recurred.

Dr. Dragstedt has pointed out what I think is one possible indication for vagotomy in gastric ulcer. If the ulcer is unusually high in the

stomach, and removal of it would require a total gastrectomy, or practically a total gastrectomy, then one is justified in considering a vagotomy. If the lesion disappears and remains healed after operation one can rest satisfied. However, if the lesion does not disappear, then one should assume that it may be malignant, and proceed with a gastric resection or a total gastrectomy if it is indicated.

In the case of *duodenal* ulcer interest in vagotomy alone as a therapeutic procedure has quieted down considerably. It seems unfortunate in some respects at least that vagotomy so promptly relieves the pain of ulcer. To have a patient who has had such pain and perhaps has been wakened several times at night for months or even for years, and to have such a patient promptly relieved of pain by section of the vagus nerves has encouraged surgeons to proceed rather rapidly with performing this operation on other patients. This striking initial response has frequently led to failure to appreciate the real importance of disturbances in gastric emptying following vagotomy which have necessitated an additional simultaneous or subsequent operation on the stomach.

How often will gastroenterostomy, pyloroplasty or gastric resection have to be done along with vagotomy in order to control gastric retention? Winkelstein of the Mt. Sinai Hospital, New York, suggests that some procedures will have to be done on the stomach in approximately 20 per cent of cases. It is my understanding that in Dragstedt's experience approximately 40 per cent of the patients in addition to vagotomy have an associated operation to assist in emptying the stomach. Consequently I think many conservative clinicians and perhaps a number of surgeons also now feel that vagotomy is of value for patients with duodenal ulcer in only a small and probably a receding group. One may delineate that group by saying that it would be one in which the individuals were young, in whom the gastric acids gave high values, in whom there were no complications, in whom the patient had intractable symptoms and in whom for some reason or other one did not wish to do a gastric resection. Under the circumstances of such a case, I think vagotomy might be considered, but one would have to keep in mind the possibility that along with it or subsequent to it some other procedure might have to be performed.

At present the real place for vagotomy appears to be in the management of gastrojejunal ulcer and particularly those which occur following gastric resection. The reasons for this opinion are, first, that effective surgical procedures now ordinarily carried out for such lesions lead to a fairly high mortality. Second, a vagotomy can be performed in these individuals without the problem of subsequent difficulty in emptying of the stomach, because if the anastomosis already is present gastric retention is unlikely. The problem of gastric emptying in patients with a partially resected stomach who have a jejunal ulcer is not one of any great prominence.

patients who have had complete vagotomy do develop frequent bowel movements but in only a few is it persistent and difficult to control. Grimson has reported a number of patients who still have persistent diarrhea some two years after vagotomy.

We feel in this clinic that vagotomy is contraindicated in patients with gastric ulcer. As clinicians we are not always able to make a definite diagnosis of gastric ulcer, even though our patients may respond to conservative medical treatment and the ulcer may disappear. We often find that we have been dealing with a gastric carcinoma which has tended to heal under medical treatment. Gastric resection is the operation of choice in such a patient.

If we have lost our enthusiasm for vagotomy, is there any patient to whom we should apply this operation? We believe that there may be a limited number of patients who are proper candidates. These are the young persons suffering with duodenal ulcer who have a very high gastric acidity and no demonstrable evidence of gastric retention. Possibly such patients are candidates for vagotomy, and apparently our best and most lasting results have been accomplished in this group. Vagotomy has been performed in patients with bleeding peptic ulcer. I am convinced that severe hemorrhage is a contraindication. I know personally of two patients who have bled to death some weeks following vagotomy.

As regards vagotomy in the treatment of large gastric ulcers high on the lesser curvature of the stomach and of persistent ulcers in the region of the pylorus which are penetrating into the pancreas, vagotomy is hazardous because these ulcers are often incapable of healing. Even though the gastric acidity is reduced and the gastric motility decreased, extensive fibrous infiltration around a large crater may prevent healing. Vagotomy under such conditions will relieve only pain and will not prevent serious complications. We have seen one such patient bleed to death.

We do believe that vagotomy is indicated in marginal ulcer as a complication of posterior gastroenterostomy or as a complication of gastric resection. It would seem from the reports in the literature and from our own experience to the present time that this is a simple means of relieving marginal ulcer. What the lasting effects will be, no one knows. Certain of these patients, if they regain acidity in their stomachs, will have recurrence of marginal ulcers with the complication in some of gastrojejunocolic fistula. For the same reason we believe that vagotomy may be indicated as an adjunct to gastric resection for duodenal ulcer, particularly in patients who have had high gastric acidity and marked increase in motility of the stomach before operation. A certain number of patients do secrete acid following gastric resection, and we hope that by doing a vagotomy in association wth gastric resection we may prevent the recurrence of acid and the formation of marginal ulcer.

QUESTIONS AND ANSWERS

DR. WILBUR: If there are any questions anyone would like to ask from the audience, you can pass them up here or just ask them orally.

QUESTION: Dr. Mathewson says that after subtotal gastrectomy, gastric acid secretion sometimes returns. The statement also was made that the same is true after vagotomy. Then he suggests that vagotomy might be done at the time of gastric resection. Why wouldn't it be better to hold vagotomy in reserve until after gastric secretion returns, and then do vagotomy?

DR. MATHEWSON: The reason is that ordinarily the evidence of the return of acid in the stomach comes with the development of symptoms, and the symptoms are usually associated with an ulcer which is present in the stoma. Those ulcers are very difficult to treat, first of all because they often cause a good deal of deformity of the stoma, and secondly because they are apt to perforate into the surrounding tissues. We feel that if we can prevent the formation of such an ulcer, we are better off than attempting to treat it after it does develop.

QUESTION: In cases of hemorrhage following vagotomy, did the vagotomy in any way contribute to the occurrence of the hemorrhage?

DR. MATHEWSON: The two patients observed with fatal hemorrhage after vagotomy had been tested with insulin and found to have no acid response. At postmortem examination, it was found that, in spite of anacidity, the ulcer had not healed. That is why I emphasized the point that we, here, believe that large, chronic, penetrating ulcers in the region of the pancreas are often incapable of healing, even though gastric acidity is reduced or abolished. These ulcers are dangerous because they may erode into large vessels and cause fatal hemorrhage. In both of these cases it seemed obvious at postmortem examination that the ulcer was large and sclerotic and there was so much fibrous tissue around it that it was actually incapable of healing.

QUESTION: What percentage of patients develop persistent diarrhea postoperatively?

DR. MATHEWSON: About 80 per cent of the patients develop diarrhea to a certain extent.

QUESTION: I said "persistent."

DR. MATHEWSON: Only about 4 per cent of the patients develop persistent, troublesome diarrhea. At least it is so reported in the literature.

QUESTION: Doctor Cheney, after gastric resection when the patient gets back to you again, what do you do for him immediately besides try to remove the psychic stimulation or disturbance which probably is a factor? Do you give a special diet or alkalies or anything like that?

DR. CHENEY: Are you assuming the gastric resection patient has symptoms or no symptoms?

QUESTION: No, no symptoms as yet. He has just returned from the operation.

DR. CHENEY: I keep these patients on the usual type of fairly full ulcer diet, that is, bland foods and perhaps feedings of five or six times a day, just as I would a patient in convalescence if the ulcer has healed without the gastric resection, as many peptic ulcers do. The patient should follow a reasonable course of treatment as regards diet and mode of living. If you believe that smoking and drinking upset the patient he shouldn't smoke or drink. I think you have to handle the patient in a manner similar to that which you use for the patient who has had an ulcer in the duodenum which has healed under medical treatment. You keep the patient on a controlled regimen indefinitely. The first patient upon whom I had a subtotal resection performed, was operated upon about fifteen years ago. I have not seen much of him since but he has gotten along very well without any ulcer trouble although he has indulged in alcoholic beverages ever since, and is able to tolerate them without any recurrence of his ulcer symptoms. So how important it is to keep the patient always on the regimen I can't tell you, but I think it is good clinical practice to keep him on a controlled regimen.

DR. WILBUR: I know of at least two patients who have been drinking heavily ever since a gastric resection for ulcer was done and secondary ulceration has not occurred.

One point that has not been thoroughly discussed is the matter of the completeness of vagotomy. Dr. Cheney, would you be willing to say a few words on the importance of doing a complete vagotomy, and how one can tell whether a complete vagotomy has been done?

DR. CHENEY: A complete vagotomy means cutting all of the vagus nerve fibers. The vagus nerves are rather readily located. In certain regions of the esophagus their course varies considerably. The position of the branches is fairly consistent in about 80 to 90 per cent of the cases. In this group the cutting of all the vagus nerve fibers is surgically relatively simple, but perhaps in 10 per cent or more there are branches which may be missed unless a careful search is made for them about the esophagus. After the operation the test of whether or not all the branches of the vagus have been severed is a test of whether or not there is psychic acid secretion. This is determined by the insulin gastric analysis test. Normally the hypoglycemia produced by insulin affects the cerebrum and produces a psychically stimulated gastric secretion and acidity. If the insulin test after vagotomy produces no gastric secretion with acid juice, presumably all vagus fibers have been severed. If the insulin test results in a secretion of acid gastric juice after vagotomy, it indicates that all the fibers have not been resected.

The test was set up as a standard procedure by Dragstedt and others. I would like to point out one fallacy in the interpretation of this test. Cutting the vagus nerves does not mean the patient will not secrete any acid juice postoperatively. It only means he will not

secrete it neurogenically or psychogenically. The fallacy is based on the assumption that almost all patients suffering from peptic ulcer have a psychogenic disorder; that basically peptic ulcer is a result of mental disturbance. I believe this is a completely erroneous assumption. You may cut the vagus nerves to control the psychic secretion of acid, but if your patient happens to be one of those quiet farmer lads with an ulcer who doesn't get psychically upset, he may still secrete acid juice!

The stomachs of many patients will respond to histamine stimulation after vagotomy. I don't think one can assume that cutting the vagus nerve by any means produces achlorhydria in all patients simply because it may do so in patients with high psychogenic acid secretion. How many ulcers may be basically due to psychogenic activity and how many may not, is another matter. A rather wide military experience with peptic ulcer has served to emphasize this point. It is noteworthy that the majority of the young adults off the plains and farms and out of the interior states who had peptic ulcer apparently did not have their peptic ulcer because they were psychoneurotic or under emotional stress or strain, nor did they fit into the usual group of patients that we all see in practice—those who make repeated visits to our offices and to the hospital clinics. There are two groups of ulcer patients, and the group that has high gastric acidity due to psychogenic activity or associated with it is presumably the group that vagotomy will help most.

QUESTION: Do you believe that the diarrhea you do see is based on the surgically produced achlorhydria, or on changes in acid production that we frequently see in practice?

DR. MATHEWSON: Apparently it is of neurogenic origin, and probably has nothing to do with the achlorhydria. Many of these patients are relieved of diarrhea by the administration of urecholin, as is often true also of the gastric retention.

DR. CHENEY: It sometimes relieves it.

DR. MATHEWSON: It is often relieved, but not always.

DR. WILBUR: I might add further that for some individuals urecholin is effective when placed under the tongue. It may not be so when given by mouth, however, because there isn't enough absorption from the stomach. One can carry along such patients by subcutaneous administration of the drug and then switch to the administration of the drug under the tongue.

DR. CHENEY: May I make one further comment. The first half dozen patients upon whom vagotomy was done on the clinic service at Stanford were operated upon about a year ago. One of this series has been in the wards this last week. He had had what we have heard is a cardinal indication for doing vagotomy. After a previous perforation and gastroenterostomy done in 1941 elsewhere, he came to the clinic ten months ago with a marginal ulcer and severe pain. A vagotomy

was done, with excellent immediate results. He is now in the ward experiencing less severe pain but with a marginal ulcer—actually a submarginal ulcer, jejunal ulcer—and a severe hemorrhage. He had never had hemorrhages before the vagotomy. This was the type of case in which everybody agrees a vagotomy is indicated. But here is one of the first six patients that we operated on, already back ten months after his vagotomy with a severe complication!

DR. WILBUR: In summary one can say very briefly that the effects of vagotomy on the stomach in the individual who has an ulcer are these: first, that the pain of ulcer is relieved; second, that there is a marked disturbance in the motility and emptying of the stomach; third, that when the vagotomy is complete there is absence of the cephalic phase of gastric secretion. One could say that clinically the operation is not indicated in patients with gastric ulcer, and that it may be indicated in some patients with duodenal ulcer, and that its principal indication appears to be for those patients who have an ulcer following gastric resection and perhaps following gastroenterostomy.

I think one can say further that the value of the procedure in patients who have a gastric resection and a vagotomy done at the same time remains to be determined, and that, finally, as Doctor Mathewson has pointed out, the operation now apparently is preferably to be done by the abdominal route because this permits one to inspect the stomach and duodenum, and also to do anything which appears to be necessary in directly attacking the lesion.

PEPTIC ULCER

The Relation of the Lesion to Symptoms and to Indications for Operation

ARTHUR L. BLOOMFIELD, M.D., F.A.C.P.

Two main types of pain occur in patients with peptic ulcer. One type is caused by penetration of the lesion through the mucosal and muscular layers of the stomach or duodenum. This pain is usually steady, and there may be tenderness on pressure; the symptoms are thought to be due to peritoneal irritation. The other and more common variety of so-called "ulcer pain" consists of epigastric discomfort, fullness or burning, perhaps with regurgitation of "sour" material, or with belching of gas. This type of discomfort often occurs at regular intervals after eating and may be relieved by taking food or alkalies. There is usually little or no tenderness, and pressure over the epigastrium may actually give comfort. This latter group of symptoms we shall refer to as "indigeston," and it is with this sort of pain only that we are concerned in the present discussion.

Two distinct and indeed opposing schools of thought have sprung up in regard to the explanation of "ulcer indigestion." In this country Palmer and his associates[1, 2] especially, have sustained the thesis, based on careful experimental work in man, that these symptoms are usually due to irritation of the ulcer by acid gastric contents, although peristalsis and muscle tension may precipitate pain if the lesion has been sensitized by exposure to acid; this view has recently been strongly supported by the studies of Bonney and Pickering[3] in England. Others, following the early work of Hurst,[4] believe that the lesion itself is usually insensitive and that symptoms arise from an abnormal state of muscular tension or spasm in the upper gastrointestinal tract. The controversy seems a difficult one to settle, even apart from its strongly partisan character, since so many of the facts may be interpreted to support either view. Aspiration of gastric contents, for example, at the height of "ulcer pain" may be followed by prompt relief.[3] Is this due to removal of acid per se, or does emptying the stomach produce a mechanical change which relieves symptoms? The entire problem of visceral pain is extremely complex, as anyone who studies the monographs of Lewis[5] or of Livingston[6] will realize, and most of the clinical literature deals with the question only superficially. Indeed the apparent discrepancies between current views

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would probably be reconciled by adequate knowledge of pain mechanisms.

But the matter is not only of theoretical interest. It is of the highest practical importance in planning treatment for the individual patient. If, for example, the indigestion of ulcer patients is caused directly by the presence of an open lesion, then it is obvious that cure will be effected only by healing or by removing the lesion. If, on the other hand, symptoms are brought about by some other indirect mechanism then a dual problem, that of dealing first with symptoms, and then with the lesion, exists. For this reason, our discussion on therapeutic indications must be prefaced by an analysis of the evidence bearing on this vexed question.

MECHANISM OF PRODUCTION OF SYMPTOMS

Against the acid irritation theory is the common observation that an ulcer may erode through the entire thickness of the stomach wall and yet, even though such a lesion is constantly bathed in highly acid gastric juice, discomfort may be entirely absent until perforation takes place. In answer to this argument the statement has been made that pain is not caused by acid unless the pain-producing mechanism is sensitive,[7] or that the crater may be filled with foreign material or granulation tissue which contains no nerve endings.[8]

Symptoms identical with those often experienced by ulcer patients may occur in people who show no evidence of ulcer by x-ray or gastroscopy and who have no occult blood in the stools.[9] Güyer,[10] for example, among 200 dyspeptic soldiers found evidence of ulcer in only 16.5 per cent. In reply to observations of this sort the answer has been made that an unrecognized ulcer probably is actually present.[3]

Symptoms may persist in identical form after surgical extirpation of the ulcer, as in the following case:

A 56 year old man (No. 181151) had complained of stomach trouble for six years. Epigastric distress came on two or three hours after meals and was relieved by foods, olive oil and magnesia. The gastric acidity was high, and x-rays showed marked deformity of the duodenal cap. At operation there was a chronic duodenal ulcer, which was excised by a Judd pyloroplasty. The same symptoms were present after operation and continued without relief, even on a strict program of acid neutralization. There was no evidence by x-ray or bleeding of recurrence of ulcer. It seems improbable that the symptoms which recurred immediately after the operation could be due to acid irritation of the ulcer, since it had been completely excised.

There are many authentic records of ulcer patients with indigestion who have a complete absence of gastric acid.[11] In discussions of such findings the claim has been made that people who put out no acid after the conventional tests do secrete when normal meals are eaten.

We have, however, studied a number of patients with verified ulcer who had only minimal amounts of secretion with a pH of 8 to 9 even after a full dose of histamine.[12]

A 43 year old man (No. A20351) complained of upper abdominal pain. He had had epigastric discomfort for years coming on one-half to two hours after meals. Symptoms varied from time to time and were to some extent relieved by smooth diet. X-rays showed a large ulcer crater on the lesser curvature. Numerous histamine tests showed complete anacidity, so acid irritation could have played no part in producing symptoms in this case. Palmer and Mutter, however, question such cases[13] since they have found with a series of histamine tests that the acid response is highly variable. This has not been our own experience.

Against the acid irritation theory the point has been made that "ulcer indigestion" is often relieved within a day or two by rest and relief from strain without any change in gastric acidity and without as yet any evidence that the ulcer has begun to heal. Brown and Dolkart[14] in this connection found no relation between degree of gastric acidity and remissions and relapses of duodenal ulcer. In answer to this position, it may be said that rest has made the pain-producing mechanism insensitive to acid irritation or that the ulcer has already begun to heal and is covered with a film of less sensitive tissue.

Very important is the fact that inflation of a small balloon in the duodenum often reproduces the patient's spontaneous pain.[15] Such pain comes immediately on inflation and disappears promptly when the balloon is deflated. The sequence of events seems conclusive evidence of cause and effect; it is not necessary to find an explanation for a latent period or to invoke temporary insensitivity of the pain-producing mechanism as one so often has to do to explain the discrepancies of the acid irritation theory. Smith and his associates,[16, 17] furthermore, have shown quite clearly that stimuli arising in the colon may produce muscular spasm in the upper gastrointestinal tract which in turn is associated with epigastric discomfort.

The observation has also been made in our clinic on a number of occasions that the patient experienced his usual pain at the moment when the observer looking through the gastroscope saw a forcible contraction of the pyloric region.[18] Hamilton and Curtis,[19] as well as Smith,[20] made similar observations with the balloon method. To these findings objection may be made that contractions of stomach and duodenum without pain constantly occur in normal people as well as in patients with ulcer, and that experiments with recording balloons in the stomach have by no means always shown a relation between contraction and pain.[21, 22] All this is true but no claim has been made that normal contraction of smooth muscle produces discomfort; witness the obvious but painless intestinal peristalsis which everyone

experiences. A dyskinesia, a conflict of waves, or an abnormal state of tension hard to identify by ordinary kymographic technic must obviously be invoked to explain indigestion under the mechanical theory. Another objection which has been raised to this view is that it does not explain the burning quality of the epigastric distress. Acid burns, the stomach contains acid, hence the burning pain should be due to acid.[23] It must be understood, however, that exquisite burning pain may be produced by distention of a hollow viscus as in our experiments[24] on the esophagus with balloons when the patients complained of such feelings as "burning sensation," "fingernail against a hot stove," or "burning, gnawing pain" and the like.

The strongest argument in favor of the acid irritation theory is the relief of pain which follows the taking of alkali. An old clinical observation, the precise sequence of events has been little studied by careful methods. Bonney and Pickering[8] have recently explored the question and point out the complexities of interpreting their results. There is, for example, often a latent period of some minutes after taking alkali (4 gm.) before pain is eased. Other observers[25] have thought that bicarbonate gave relief after the gas which is generated has been expelled, indicating an altered state of tension rather than direct neutralization. Sometimes patients become comfortable after doses of alkali too small to effect neutralization of a large quantity of highly acid gastric contents (1 gm. $NaHCO_3$ neutralizes 75 cc. of 0.1N HCl).[20] Furthermore, alkalies which do not liberate gas may also relieve, and so may water, small amounts of food, and on occasion, acid itself. Alkali, rarely, even makes symptoms worse. We have seen a patient whose indigestion was eased by a spicy sauce; presumably some abnormal state of tension was relieved by this condiment. The whole question requires much more critical study. Finally, in this connection, the observations of Wilson[27] are of interest. Patients with duodenal ulcer were watched under the fluoroscope after a barium meal at a time when pain was present. It was found that relief followed the forcing of gastric contents into the duodenum by manual pressure on the abdomen in thirteen of sixteen cases, even though the material in the stomach had an acidity of from 68 to 108. Wilson concluded that relief of pain was due to relaxation of the musculature of the duodenal caput. One should also mention the interesting observations of Steinberg and Starr[28] on experimental ulcer. They found that if a ring of muscle was excised around the area where ulcer usually occurred no mucosal breakdown took place despite the presence of highly acid secretions.

Finally, it should be noted that symptoms indistinguishable from the indigestion of ulcer patients may be produced by obvious mechanical disturbances such as hiatus hernia and duodenal polyp.

The reader may draw his own conclusions from the above analysis. It would be vain to insist that acid irritation of nerve endings never

plays a part in ulcer indigestion, on the other hand, some of the arguments which we have outlined make it clear that pain must often be produced by other mechanisms However, it seems probable that the lesion, even if not directly painful, may serve as a "trigger zone" which can cause an altered state of muscular tension or spasm which in turn is immediately responsible for the indigestion symptoms Such symptoms, as clinical experience constantly shows, may be precipitated in identical form by other trigger points—a diseased gallbladder or appendix, a disturbance of the colon as shown by Smith,[17] or indeed by some remoter influence That even cortical impulses may be the source of indigestion reflexes is clear to any one who has seen the symptoms disappear when strain or worry has been removed This was dramatically illustrated by experiences in the armed forces during the recent war

At any rate, on the basis of the above facts, *it is clear that in practice one must consider relief of patient's symptoms and elimination of the ulcer as two separate problems with distinct indications* Once this elementary concept is firmly grasped the doctor will find that the planning of treatment becomes relatively simple

COMPONENTS OF PEPTIC ULCER SYNDROME

We are now in a position to analyze the various components which enter into the peptic ulcer syndrome and to discuss the therapeutic implications The problem is best visualized by means of a diagram such as Figure 70 What is to be said, as we pointed out above, represents what seems to us the most logical conclusions from the available evidence, but much is not capable of final proof at the moment

Our point of departure is the concept that a certain constitutional basis is a prerequisite for the development of peptic ulcer The subject is comprehensively reviewed by Kanevsky [29] Genetic influences have been held to play a part, and certain forms of body build[30] or of psychological type[31] have been claimed to be significant although there are conflicting opinions [32] Peptic ulcer has been said to run in families[33] and it has been found in identical twins [34] Be this as it may, it is common clinical experience that certain individuals tend to have indigestion and to develop ulcer even with careful safeguarding, whereas other people display no tendency to the peptic ulcer syndrome even under the worst conditions of nervous stress and bad dietary habits They may break down with other symptoms such as those of functional cardiovascular disease but they appear to be immune to gastroduodenal disabilities

This does not mean that everyone who has the constitutional basis will necessarily develop clinical disease On the contrary, some aggravating circumstance is usually required before symptoms actually appear Of these (see Figure 70) psychological disorders probably head the list [35] The influence of strain, tension, fear and worry in

precipitating indigestion or indeed actual ulceration is observed every day in the clinic;[36] the careful studies of Wolf and Wolff[37] with their gastric fistula subject have clearly shown the changes which occur in the gastric mucosa under emotion,[38] while Draper[39] and others have connected the more drastic accidents of peptic ulcer such as bleeding and perforation with emotional upsets. The high incidence of digestive symptoms and of ulcer in military personnel illustrates again the role of the emotions in promoting these disorders.[40, 41]

Of great importance also are bad eating habits (Fig. 70). With many people, symptoms can be precipitated by the bolting of food, by eating when under stress or excitement, by overeating or by taking

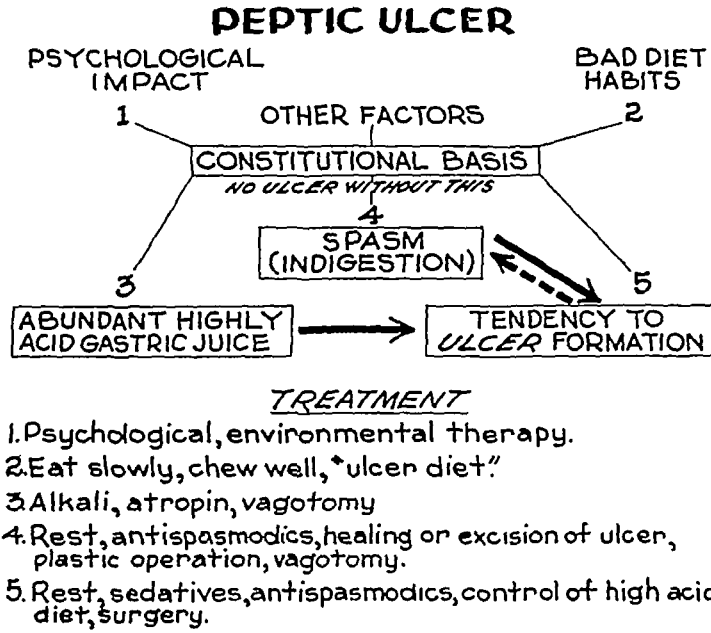
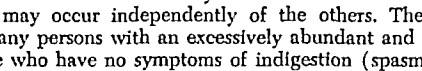


Fig. 70.—Factors of importance in the peptic ulcer syndrome.

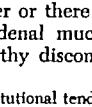
certain foods. In our experience, the last item is the least important; it is of more consequence how we eat than what we eat. The interesting observations of Welch[42] on the gastric feeding reflex show that the empty stomach expands so as to nicely accommodate food which is slowly introduced; rapid filling leads to spasm which is obviously the precursor of indigestion symptoms. We showed the same thing by inflating a balloon in the stomach. If air was introduced slowly, 500 cc. or more could be accommodated without discomfort but rapid forcing in of even 100 to 200 cc. resulted in pain.[15]

We shall not attempt to catalogue more factors which may precipitate symptoms in predisposed individuals; no doubt there are many of varying importance in different people.

Turning now to the actual components of the "ulcer syndrome," we find set down in the diagram "abundant highly acid gastric juice," "spasm," and "tendency to ulcer formation." The important point is that these are all the common expression of the underlying disorder, although as will be seen there may be certain interrelations, and one or another may occur independently of the others. There are, for example, many persons with an excessively abundant and highly acid gastric juice who have no symptoms of indigestion (spasm) and who show at the moment no ulcer formation. Others may have spasm (indigestion) without actual ulcer or there may be a tendency to breakdown of the gastric or duodenal mucosa with ulcer formation in people who have no noteworthy discomfort at the time. The above concept



differs from the acid irritation theory of ulcer which may be represented as follows:



Turning again to Figure 70, high acid secretion is shown as occurring independently of ulcer formation. It would be unwarranted, however, to suppose that a continuously excessive and highly acid secretion plays no part in promoting breakdown of the gastric or duodenal mucosa. Indeed some believe that an actual peptic digestion takes place. The situation is, however, not nearly as simple as would appear. In the first place a highly acid gastric juice is not necessarily abnormal and in studying large numbers of healthy people without digestive symptoms, distribution curves show that in at least 70 per cent an acidity of 100 or higher is attained after histamine stimulation.[43] Even with basal secretion, when no test meal or stimulus is used, values of over 100 are not uncommon.[44] To be sure, most of these people do not have the continuous highly acid night secretion which has been thought of so much importance in promoting ulcer. It would be unreasonable to suppose, however, that nature has not provided some protection against acid for those parts which are normally bathed in it; indeed the ease with which ulcer can be produced in the intestine by diverting acid into a region not naturally exposed,[45, 46] seems to support such a view. The gastric mucosa may possess some special resistance to acid or to peptic digestion; possibly the secretion of mucus protects. The abundant, very acid gastric juice

of some ulcer patients contains practically no mucus and the values for free and titratable acidity may differ by only a few degrees.

In respect to the healing of ulcer in the presence of acid, we studied a series of patients who received no treatment except rest and simple diet. No alkali was given. It was found that ulcer, either of stomach or of duodenum, might heal rapidly or slowly in the presence of either high or low basal acidity.[48] One patient with a large gastric ulcer (shown to be benign when it was finally excised), and with basal anacidity, failed to show healing in three months. Another, with basal acidity of 120, apparently healed a deep duodenal ulcer in eight days. Without laboring the point, it is clear that the presence of acid as such is not the whole story in explaining the breakdown and healing of the gastric and duodenal mucosa.

Passing, in Figure 70, from the question of acid to "spasm," the ulcer once formed may, as indicated by the arrow, act as a trigger zone which promotes some disturbance of tension or motility with consequent symptoms of indigestion. Conversely, spasm, as shown by the studies of Wolf and Wolff,[49] probably plays a large part in promoting mucosal breakdown. In their gastrostomy subject, Wolf and Wolff actually observed spasm and hyperemia to be followed by small erosions.

The above explanation of "peptic ulcer" may then be summarized as follows:

Certain individuals with a constitutional predisposition tend to develop peptic ulcer, especially under certain stresses (psychological, dietetic). These people usually secrete an abundant highly acid gastric juice. They also tend to have disturbances of muscular tension in the upper gastrointestinal tract ("spasm") which produce symptoms of indigestion—epigastric distress, fullness, burning, and the like. They have a gastroduodenal mucosa which readily breaks down into ulcer. These major features are the common results of the constitutional tendency and, while they have some interrelationships, one cannot be explained solely as the result of another.

If these concepts are accepted then the planning of treatment becomes relatively easy. *One must keep constantly in mind that relief of symptoms and healing of lesion must be thought of as two separate objectives which will not necessarily respond to the same measures.*

Relief of symptoms does not mean that the ulcer is healed; healing of ulcer does not guarantee freedom from those vices of motility which produce indigestion, or from recurrence of mucosal breakdown.

TREATMENT PLANNING

An essential preliminary to the planning of treatment is a precise evaluation of the precipitating factors in the case. As shown in the diagram (Fig. 70) if psychological stresses are important they must

be dealt with (Item 1). If bad eating habits or unsuitable diet are paramount then they must be corrected (Item 2), and in that case the psychiatric approach may be useless. Or, there may be both psychological and somatic problems in the same patient, the relative importance of which the doctor must assay. Turning next to the abundant highly acid gastric juice so often present, whether any direct attack such as resection[50] is indicated here (Item 3) depends on one's views as to the part played by acid in the whole picture. Alkalies, atropine and perhaps vagotomy make up the armamentarium. There is no evidence that rest or psychotherapy has any particular effect on the degree of gastric secretion. Symptoms of indigestion, which we believe to be usually mediated by "spasm" (Item 4), yield above all to rest, in the sense of relief from strain, physical and mental. Antispasmodics may help and vagotomy is promptly followed by relief. The value of this procedure is, however, not yet fully defined.[51, 52, 53, 54] Healing of the ulcer may do away with a trigger point, but indigestion usually abates before the ulcer is healed. Finally (see Item 5) the tendency to actual ulcer formation may be controlled by some or all of the measures already enumerated. When should surgery come into the picture? Aside from the obvious indications of perforation, intractable bleeding and pyloric stenosis, operation is in order to remove a lesion which may be malignant, to remove a lesion which may be a trigger zone for indigestion reflexes after medical treatment has failed, or to attempt to break up indigestion reflexes by a plastic operation on the pylorus or by vagotomy. Some feel it is important to reduce acidity by gastric resection. As long as surgeons maintain the ancient view that the open ulcer is the direct and only cause of all the symptoms and that the various methods of elimination of the ulcer are the whole problem, confusion will continue and unsatisfactory results will be obtained.[55]

A more detailed statement about our plan for treating peptic ulcer patients with indigestion symptoms but no complications, such as bleeding or obstruction, may be presented at this point. Since we believe that spasm plays a major part in the immediate production of symptoms, *relief of strain and tension* is of the utmost importance. Whether this is to be accomplished by bed rest in a hospital, by a fishing trip, by simple advice, or by technical psychiatric measures, must be decided by the doctor in the individual case.

Next to be considered is *diet* which as everyone knows has always been regarded as the central feature of ulcer therapy. Just what sort of a diet program will be advised depends somewhat on one's views as to the cause of ulcer and of symptoms. The popular "Sippy" regimen, for example, was based on the view that acid is all-important; the "Sippy" plan is aimed at controlling gastric acidity throughout the twenty-four hours by frequent feedings, and by administration of alkalies. Since we feel that spasm is at least equally important we lay less stress on constant alkalinization which also has the disadvantage

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of producing alkalosis on occasion and constitutes a psychological hazard in some people since their minds are kept constantly centered on their troubles by the frequent doses of medicine. We feel that the way one eats is of the greatest importance; one should always eat very slowly, chew well, and sip liquids. One should never eat when under stress, and business discussions and excitement of any sort should be avoided at meal times. The stomach should never be loaded with a huge meal at any one time. There should be three small meals with intermediate nourishment three times a day consisting of 100 to 200 cc. of milk or of half milk and half cream depending on the patient's state of nutrition. The meals should be small (total calories per day just enough to meet energy requirements) and should consist of simple food plainly cooked. All very coarse and tough articles should be excluded (e.g., corn on the cob, gristle of meat). All very highly seasoned and spiced articles are to be avoided (e.g., enchilladas). Finally, all very rich and greasy foods should be avoided (e.g., a very greasy pork chop). For breakfast, then, there would be a choice of strained fruit juice, strained cereals, well-cooked eggs, *crisp* bacon, toast, milk or coffee. The other meals would consist of plain broths or cream soups, lean meat, fish or chicken, plainly cooked, well cooked starchy vegetables and puréed green vegetables. For dessert there would be jellies, junket, custard, plain sponge cake, and plain vanilla ice cream. If the patient has severe discomfort when first seen, a few days during which he gets nothing but 100 cc. of half milk and half cream every two hours when awake are advisable before starting the diet outlined above. A compound vitamin capsule once daily should be given if there is any question of vitamin deficiency.

It is our practice to give some sort of "antispasmodic." Belladonna has the advantage not only of relaxing spasm but of cutting down the volume of gastric secretions and to some extent the degree of acidity. It should be pushed until symptoms of full dosage appear such as dry mouth. Much more than the conventional few drops thrice daily may be necessary. We see no objection to fairly frequent doses of alkali, and at the moment prefer one or another of the colloidal antacids such as an aqueous suspension of aluminum hydroxide, one or two teaspoonfuls every two to four hours in milk or water, when awake. This material may also be obtained in tablet form. There is no objection to the taking of a dose of bicarbonate of soda at the time when distress is present if relief follows. Most people with peptic ulcer are tense and a small dose of phenobarbital 0.032 gm. (½ grain) three times daily is helpful.

Some such program is the backbone of our treatment until the ulcer is healed and symptoms have been relieved. With intractable symptoms or failure of the ulcer to disappear, one faces complicated decisions as to resection or vagotomy which cannot be discussed in detail here.

Illustrative Case History.—The above principles are illustrated by the following case report.

A 46 year old office worker was seen in September 1946, with the complaint of indigestion. There was nothing remarkable in his past history. He was a highly neurotic and introspective man, and he described many minor complaints in great detail. The clinical difficulty, however, was that for many years he had had indigestion featured by soreness and burning in the epigastrium. The symptoms came in bouts, better at times, but always worse when he was under strain. He had tried all sorts of diets and got partial relief from mush and milk. He lived alone in a small hotel, and took his meals there. He tried not to eat in a hurry. He had always been the worrying type. He was apprehensive about his old mother for whom he was financially responsible. He was in the advertising business and worked under considerable strain. He was meticulous about his duties.

Examination showed a sallow, flabby man, slightly overweight. The heart and lungs were clear. Nothing of importance was noted in the abdomen. There was no tenderness on pressure. He "did not have time" to stop his work for x-ray examination, so a mixture of belladonna and bromide was prescribed, and he was urged to eat slowly and to chew well, and to take a simple diet avoiding coarse, highly seasoned and greasy foods. The importance of trying to lessen nervous strain and tension was pointed out.

Two weeks later, he told us there had been practically no indigestion, but he talked at length about other minor complaints. On December 16, he reported that his indigestion was as bad as ever in spite of adherence to the prescribed regimen. He was working hard and could take no time off for a thorough rest. He was advised to take only small amounts of milk for a few days; this gave little relief. For the next three months his symptoms varied but he was uncomfortable most of the time in spite of various diets, alkalies, belladonna and sedatives. On March 4, 1946, he reported a specially severe flare-up of symptoms with almost constant epigastric burning distress. He was brought into the hospital where physical examination again was not remarkable. His gastric juice, however, was among the most acid we have ever encountered. There was a free flow of large quantities of gastric secretion, and even without any stimulus such as a test meal or histamine the total acidity was 140. This value increased only slightly after histamine, showing that this man's stomach was constantly secreting at nearly its maximum capability. The juice had the appearance of spring water and there was no visible mucus. The stool showed no occult blood, and there was no anemia, but x-rays were reported as follows: "The duodenal cap is always irregular, and cannot be emptied out by pressure over it. Two flecks of barium remain in the cap when the cap is pressed upon. The appearance is that of duodenal ulcer. At six hours the stomach is not empty. There is about 20 per cent of residue. The two tiny spots are seen in the cap also at the six hour examination. At twenty-four hours, the flecks of barium are no longer present in the cap."

The patient was persuaded to stay in the hospital for two weeks where he received classical medical therapy—rest, sedatives, alkalies, antispasmodics, and rigid "ulcer diet." He remained tense, however, he continued to worry about his work, and did not seem really relaxed. His stream of talk about inconsequential details of symptoms was unabated. His indigestion became less marked, but it was clear that nothing fundamental was being accomplished.

Comment on the Case.—Here then is a case which illustrates a stubborn tendency to duodenal ulcer in a person who seems constitutionally predisposed. This man consistently secreted a large amount of thin, very highly acid gastric juice. He had persistent indigestion, which clearly was associated with enough spasm to produce at times

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A 46 year old office worker was seen in September 1946, with the complaint of indigestion. There was nothing remarkable in his past history. He was a highly neurotic and introspective man, and he described many minor complaints in great detail. The clinical difficulty, however, was that for many years he had had indigestion featured by soreness and burning in the epigastrium. The symptoms came in bouts, better at times, but always worse when he was under strain. He had tried all sorts of diets and got partial relief from mush and milk. He lived alone in a small hotel, and took his meals there. He tried not to eat in a hurry. He had always been the worrying type. He was apprehensive about his old mother for whom he was financially responsible. He was in the advertising business and worked under considerable strain. He was meticulous about his duties.

Examination showed a sallow, flabby man, slightly overweight. The heart and lungs were clear. Nothing of importance was noted in the abdomen. There was no tenderness on pressure. He "did not have time" to stop his work for x-ray examination, so a mixture of belladonna and bromide was prescribed, and he was urged to eat slowly and to chew well, and to take a simple diet avoiding coarse, highly seasoned and greasy foods The importance of trying to lessen nervous strain and tension was pointed out.

Two weeks later, he told us there had been practically no indigestion, but he talked at length about other minor complaints. On December 16, he reported that his indigestion was as bad as ever in spite of adherence to the prescribed regimen. He was working hard and could take no time off for a thorough rest. He was advised to take only small amounts of milk for a few days, this gave little relief For the next three months his symptoms varied but he was uncomfortable most of the time in spite of various diets, alkalies, belladonna and sedatives. On March 4, 1946, he reported a specially severe flare-up of symptoms with almost constant epigastric burning distress. He was brought into the hospital where physical examination again was not remarkable. His gastric juice, however, was among the most acid we have ever encountered. There was a free flow of large quantities of gastric secretion, and even without any stimulus such as a test meal or histamine the total acidity was 140. This value increased only slightly after histamine, showing that this man's stomach was constantly secreting at nearly its maximum capability. The juice had the appearance of spring water and there was no visible mucus. The stool showed no occult blood, and there was no anemia, but x-rays were reported as follows: "The duodenal cap is always irregular, and cannot be emptied out by pressure over it. Two flecks of barium remain in the cap when the cap is pressed upon. The appearance is that of duodenal ulcer. At six hours the stomach is not empty. There is about 20 per cent of residue. The two tiny spots are seen in the cap also at the six hour examination. At twenty-four hours, the flecks of barium are no longer present in the cap"

The patient was persuaded to stay in the hospital for two weeks where he received classical medical therapy—rest, sedatives, alkalies, antispasmodics, and rigid "ulcer diet." He remained tense, however, he continued to worry about his work, and did not seem really relaxed. His stream of talk about inconsequential details of symptoms was unabated. His indigestion became less marked, but it was clear that nothing fundamental was being accomplished.

Comment on the Case.—Here then is a case which illustrates a stubborn tendency to duodenal ulcer in a person who seems constitutionally predisposed. This man consistently secreted a large amount of thin, very highly acid gastric juice. He had persistent indigestion, which clearly was associated with enough spasm to produce at times

demonstrable gastric retention. His duodenal mucosa, evidently, broke down easily, and ulcer formation was demonstrated by x-ray. As the sequel will show, however, there is no strong evidence that the ulcer itself caused his indigestion symptoms; that the intensely acid gastric juice together with spasm promoted breakdown of his mucosa does seem highly probable. As to predisposing factors, diet, and eating habits were good and appeared to play little if any part. There was great nervous strain, however, in a lonely conscientious meticulous man who worried constantly about his work, his mother and his health.

Treatment.—The classical approach would be to assume that the ulcer was the direct cause of all this man's symptoms and to remove it if healing did not take place under medical therapy. On the basis of our initial discussion, however, it is clear that such a position may not be sound since the small duodenal ulcerations were obviously not the direct cause of all his symptoms, but rather an incident in a more widespread disorder. There was no reason to believe that the extirpation of the ulcer would in itself yield a cure since the man had the sort of duodenum which would probably break down again under the influence of spasm and hyperacidity; nor was there reason to believe that healing of the ulcer would eliminate his indigestion.

The problems of dealing with his symptoms on the one hand and his lesion on the other were therefore considered separately. It seemed that "spasm" was the immediate precursor of symptoms and that this could best be allayed by relief from nervous strain and by "antispasmodics." While very transient improvement was obtained, his psychological distemper was too profound to be much altered and in the end nothing noteworthy was accomplished by these means. We did not believe that his high acid was the direct cause of symptoms nor did we know of any nonsurgical means of reducing acidity, except temporarily by alkalies. Even when large doses of alkali were given there was no satisfactory relief, probably because symptoms came from spasm and not directly from acid.

It was finally decided to advise operation. The purpose was not primarily to remove the ulcer, but to make a wider pyloric opening with the idea of reducing pylorospasm and to promote regurgitation of alkaline duodenal contents into the stomach. Operation was performed on March 24. On opening the abdomen a large stomach presented. Some fibrous bands were attached to the anterior surface of the duodenum where definite evidence of ulceration was found. The pyloric ring was not constricted. The duodenum was easily mobilized, the area showing signs of ulceration was excised and a pyloroplasty was done. The resected specimen showed two small but fairly deep ulcers and the mucosa in general showed signs of chronic inflammation.

The patient made an uneventful recovery except for a slight wound infection. During convalescence, however, he became very nervous

and concerned over missing his work. On leaving the hospital, he was placed on the full medical regimen previously described. Three weeks later he returned, complaining of the old symptoms which were essentially unchanged, in spite of the fact that the area of overt ulceration had been removed. It seemed clear, therefore, that he still had enough spasm to cause indigestion, and something else must be done to relieve this. It was difficult now to obtain stomach juice without admixture of bile, but the acidity was essentially unchanged. X-rays showed no gastric retention and the site of the anastomosis seemed in order. This was verified by gastroscopy. On May 20 transthoracic vagotomy was done with the idea mainly of relieving his [illegible] increasing motility. His symptoms disappeared immediately after operation and so far (July, 1947) have not reappeared. X-rays after vagotomy showed a smooth, relaxed stomach but emptying was quite probably because of the wide stoma. Basal gastric acidity ten days after vagotomy was 80 instead of 140 as found before the first operation. The quantity of secretion could not be measured accurately but was considerably reduced.

In summary, then, this case history illustrates [illegible] tion of the principles outlined in our preliminary [illegible] that, in planning treatment, relief of symptoms [illegible] lesion must be considered as distinct problems, and that removal of the lesion does not solve the whole problem, the complications of which are not yet fully understood.

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THE MEDICAL MANAGEMENT OF MASSIVE UPPER GASTROINTESTINAL HEMORRHAGE

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SYMPTOMS AND SIGNS

THE symptoms and signs of massive upper gastrointestinal hemorrhage may be divided into those caused by the loss of blood and those for which the underlying disease is responsible. A tarry stool may be the initial indication of hemorrhage. This may be preceded by a sudden desire to defecate, accompanied by weakness, chilliness and nausea. Syncope may occur during or soon after defecation. If the loss of blood exceeds 350 cc. there may be an increase in the pulse rate and pallor.

When the loss of blood becomes large enough to disable the ordinary mechanism for the maintenance of blood volume the symptom of shock predominates. This may occur immediately after a large hemorrhage or after several hours when the blood volume may drop without further blood loss (secondary hemorrhagic shock). The arterial blood pressure falls to 80 mm. of mercury or less; the pulse is rapid, small, thready; the skin is cold and clammy. There are air hunger, rapid shallow breathing, restlessness and thirst. The hemoglobin and erythrocyte count may not reflect the changes in the blood volume until several hours later when dilution of the plasma from the tissues produces a lowering.

A previous history of pain compatible with the diagnosis of peptic ulcer may or may not be present in patients who have bleeding from the ulcer. When pain exists as a prodromal symptom it often disappears with the advent of hemorrhage. Although some authors[1] believe that a history of a previous hemorrhage points toward the diagnostic probability of ulcer, my experience suggests that repeated hemorrhage may occur with equal likelihood in hepatic cirrhosis with varices. Cirrhosis may be suggested by a history of alcoholism or of dietary deficiency or by the presence of ascites, an abdominal collateral circulation, a large liver or spleen, spider hemangiomas or jaundice.

INDICATIONS FOR SURGERY

A good conservative regimen is the best treatment for over 95 per cent of patients with massive bleeding from the upper gastrointestinal tract. Operation is needed in less than 5 per cent of the cases, but is indicated in certain patients with gastric or duodenal ulcer. In general, the indications include patients over 45 years of age who have a

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red blood count of less than 2,500,000, who have a history of repeated bleeding from a proved ulcer or who continue to vomit or to bleed. The operation of choice is a gastric resection which includes the ulcer; it is done preferably within twenty-four hours after the onset of hemorrhage or as an interval procedure. The concept of the ideal case for resection is that in which the hemorrhage comes from a sclerotic artery in an indurated ulcer bed. Superficial hemorrhage, even in an old ulcer, does not require that gastric resection be done. There is no reason to think that partial gastrectomy will prevent further development of such lesions in the remaining stomach or duodenum.

The great difficulty lies in the selection of cases for operation. Here, as in the medical management of the condition, emphasis must be placed on the importance of individualization of treatment. The surgeon feels, rightly, that he should have the patient for operation in as good condition as possible. However, operation should not be done early—or at all—to improve on previously poor surgical statistics, or because the previous nonsurgical therapy has not been good.

The following case is presented to illustrate the hazards of the management of the individual patient:

A 63 year old man was admitted to the San Francisco Hospital for the fourth time in December 1945. In 1933 he had had pulmonary tuberculosis followed by calcification of the lesion. In 1925 he was operated on for a perforated peptic ulcer. In 1941 he was seen and treated for epigastric distress, nausea and vomiting which were thought to be caused by a peptic ulcer. In 1944 he was admitted because of hematemesis. A duodenal ulcer was diagnosed by x-ray. During the three months preceding the last admission he had increasing indigestion, nausea and vomiting with a moderate amount of hemorrhage for three days. By x-ray the duodenal cap was deformed but no ulcer was demonstrated. The hemoglobin dropped from 90 per cent (Sahli) to 74 per cent; the erythrocyte count remained about 4,500,000 over a period of two weeks. The blood urea was 51 mg. per 100 cc. It was decided to do an interval operation because the patient was thought to have an ulcer of the duodenum with recurrent hemorrhage and obstruction. At surgical exploration the duodenum just distal to the pylorus was narrowed and adherent to the pancreas but no induration indicative of a recent ulcer could be identified. The distal two-thirds of the stomach was resected and a Polya type anastamosis was performed. The pathological specimen demonstrated chronic gastritis and duodenitis with an area of fibrosis in the duodenum probably related to a previous episode, but no ulceration. There were hyperemia and edema of the duodenum which may have been related to the hematemesis. The patient recovered uneventfully.

In this case were present most of the criteria considered as indications for operation and yet at operation no ulcer and no bleeding point could be demonstrated. It seems most likely that the hemorrhage came from the congested mucosal surface. The patient had recovered from similar episodes before. There was no assurance that another would not occur.

MEDICAL MANAGEMENT

The medical management of massive gastrointestinal hemorrhage includes minimal activity of the psyche and of the gastrointestinal

old man who was admitted to the eye service for an anterior staphyloma. The diagnosis of ulcer was not suspected. Death occurred during an attack of what was thought to be pulmonary edema. Autopsy showed an ulcer of the lesser curvature in which was a large thrombosed necrotic-walled artery. This and the previous case are illustrative of the patients who die too quickly after a massive hemorrhage for any treatment to be of help. Resection of the bleeding area could be life-saving if operation could be performed—but such patients commonly die without a diagnosis.

The second of the fatalities among the patients with gastric ulcer was a 62 year old woman who had a fifteen year history of ulcer symptoms including three to four episodes of bleeding. She had been hospitalized numerous times. The final entry occurred five months before death and was occasioned by a left hemiplegia. She also had a severe hypertension and arteriosclerosis. She was a difficult patient to feed properly and vegetated for long periods. Despite all this she survived five months, to succumb suddenly to a massive hemorrhage from a large artery contained in the wall of an ulcer on the lesser curvature of the stomach.

Two of the patients died postoperatively. One of these had had a previous perforation. Both deaths occurred following pyogenic complications some time distant from the gastric resection.

Among these six deaths there was only one which occurred in a patient who could be said to be on a good medical regimen. A 54 year old Japanese was admitted for a first attack of hematemesis. The pulse was 128, the blood pressure 120/92, the hemoglobin 54 per cent (S), the erythrocyte count 2,490,000, the urea 78 mg. per 100 cc. of blood, the serum protein 4.95 gm. per 100 cc. No food was given for twenty-four hours. After that he was placed on a Sippy diet. On the fourth hospital day he was found on the floor in coma as the result of a large fresh hemorrhage. Transfusion was done as soon as blood could be found. He was seen by the surgical consultant within a few hours but deemed inoperable. He died thirty hours after he had collapsed. At autopsy there was found an ulcer of the lesser curvature with a thickened protruding sclerotic artery. There is no question that a gastric resection at admission could have removed the bleeding artery.

The problem is to select properly the cases for operation. This was the single death among the thirty-three patients given conservative treatment on the medical wards. On the other hand, among seven patients treated by gastric resection there were two deaths. It is to be concluded that the overwhelming majority of the cases may be treated conservatively. Most of the patients with lesions, which at autopsy seem to be of a type best handled by resection, are inoperable when first seen by the physician or are never seen by a physician because they bleed to death so quickly.

CONCLUDING REMARKS

The majority of patients who have massive upper gastrointestinal hemorrhage bleed from a peptic ulcer. Among the patients admitted to a city hospital at the present time a high proportion also will bleed from esophageal varices complicating cirrhosis of the liver. The immediate treatment should include the relief of shock and the restoration of the blood volume. A good conservative regimen provides the best treatment for most patients with bleeding peptic ulcer, but individualization of treatment is all-important. A small series of cases is presented in which there is no evidence that surgery would have been of further benefit.

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of the peculiar muscular configuration of that area where the descending longitudinal musculature of the esophagus divides into fasciculi leaving only circular muscular fibers in support of the stomach wall[56] which may be further weakened by the penetration of many blood vessels at this point.[33] It has been argued also that the anatomically weakened cardia is pressed upon by food as it enters the stomach.[2, 6, 13] Recurrent increases in intragastric pressure resulting from cough, pyloric obstruction, pregnancy, vomiting, or prolonged constipation with straining might be expected to cause pulsion diverticula in the cardiac region of the stomach;[7, 22, 31] or elsewhere if the gastric wall were weakened by trauma, foreign body, inflammation, ulcer or malignant change.[14, 19,45] Wigby[55] found that sections of diverticula showed a thick mucous membrane and a thin muscle wall.

Certain dissenting voices have been raised. Alvarez was unable to cause outpouching of the wall in the fresh stomach of the dog and cat by increasing intraluminal pressure.[51] Bockus[5] finds local weakness of the wall an unsatisfactory explanation for congenital diverticula; Eusterman and Balfour[14] feel that it may be a contributing factor. Gastric ulcer has often been cited as a contributing factor to diverticulum, but it must be remembered that in the great majority of cases[26] the two conditions are not coexistent.

Location.—Diverticula of the stomach, particularly the congenital variety, are found principally on the lesser curvature of the stomach, toward the posterior wall, within a few centimeters of the cardiac opening of the stomach;[34] Templeton[50] believes that true diverticula elsewhere in the stomach must be very rare; certainly in reviewing the literature one is struck with the rarity, in illustrative x-rays, of diverticula at other sites.

If all types of diverticula are included, their distribution is more diffuse. Martin[26] found sixty-one of 103 instances at the cardia; of twenty-five on the lesser curvature, one was in the midportion and fourteen in the prepyloric area; of nine on the greater curvature, five were in the midportion and four prepyloric; the position of the remainder was poorly defined. Rivers and his associates[41] found 43 per cent at the cardia, 43 per cent near the pylorus, and 14 per cent in the midportion of the stomach. Tracey[51] reported thirty-five cases from the Lahey Clinic of which twenty-seven were in the cardia, three were prepyloric and four were on the anterior and one was on the posterior wall in undefined positions; Reich's eight cases[35] were on the posterior wall in the cardia; Shiflett[47] found 65 per cent in the cardia, 23 per cent prepyloric; cases have been described in which the stomach contained two or more diverticula[14] sometimes in association with diverticula in the duodenum or colon.

Size.—Diverticula vary in general from pea to plum size; their diameters ranging from 0.1 cm. to 10 cm., with an average of 3 cm.[14] Most are 1 to 6 cm. in diameter at the widest portion, and connected

with the body of the stomach by a neck or pedicle which may vary considerably in length but is usually smaller in diameter than the largest width of the diverticulum, so that the outpouching has a mushroom-shaped silhouette on x-rays.

The size of the opening into the stomach is important as the patient's symptoms may be dependent upon the amount of material retained in the sac and its discovery by x-ray upon the opaque medium which is allowed to enter.[17] In general, the ostia vary from filiform-size to 3 cm., but this opening may be narrowed by inflammatory changes usually resulting from retention of decomposing food, or its mouth on the mucosal side may be obscured by gastric folds. Tracey[51] reports the case of a woman of 31 whose prepyloric diverticulum, demonstrated by opaque meal, caused recurrent obstruction yet could not be demonstrated by careful subsequent examinations, including two laparotomies. It was discovered eventually that the tiny ostium was covered by a hemorrhoid-like tag of mucous membrane.

Pathological Considerations.—In most diverticula the mucous membrane appears intact,[53] but there may be erosions of the surface with bleeding or inflammatory changes in the wall with scarring and thickening.[49] Acute diverticulitis, gangrene, perforation or local abscess, familiar entities in diverticulosis of the colon, have not been described in gastric diverticula, perhaps because of the greater motility, better blood supply, and fewer bacteria of the latter organ. Diverticula, particularly when inflamed, may become adherent to adjacent organs. Telford[40] reports a large diverticulum of the cardia with its base embedded in and receiving an artery from the pancreas.

Adenomas, myomas, sarcomas, carcinomas and precancerous lesions may be found in the wall of a diverticulum. It seems likely in view of experience elsewhere in the body, that retained food particles and the resulting chronic inflammatory reaction may predispose to malignant change,[6, 12, 24] a cogent reason for the prophylactic removal of small-necked diverticula.

Symptoms and Signs.—Although the majority of gastric diverticula are asymptomatic, and many symptoms now attributed to them may be the result of associated disease, there is little doubt that diverticula may in themselves produce symptoms which disappear upon their drainage, invagination or removal. It is logical to suppose that most manifestations are the result of gastrospasm induced by retention of food in the diverticular sac plus diverticulitis.[52]

At the Mayo Clinic[14, 41] 64 per cent of fourteen proven cases were asymptomatic but 29 per cent had symptoms apparently due to the diverticulum; Shiflett[47] found 18.8 per cent of forty-three cases without symptoms, 40.5 per cent with symptoms due to associated disease, and 34.9 per cent with no accountable lesion other than the diverticulum; Martin[26] noted no direct connection between the diverticulum and symptoms in 49 per cent of 103 cases, collected from the litera-

eight hour films. Tracey[51] found retention in eleven of twenty-seven cases: in one case for one hour, in one for three hours, in six for six hours, and in three for forty-eight hours; he advises the use of rugar (Ba-mineral oil mixture).

8. The mucosal pattern should be soft, well defined and regular and show no sign of irritation. Well defined rugae may lead right up to the diverticulum. Irregularity in the walls may mean malignancy.[51]

9. The sac may occasionally be emptied by changing the position of the patient; this may indicate the most favorable position for therapeutic postural drainage.

Roentgenological *differential diagnosis* involves:

1. Penetrating ulcer: location usually in the lower portion of the stomach, converging prominent folds, spasm, concave indentation of adjacent mucosa, tenderness on pressure, incisura on opposite wall,[7] ulcer history.

2. Malignant disease: loss of surrounding mucosal pattern, infiltration of area with rigidity, "subtraction defect,"[37] distorted air bubble, lack of peristalsis, fixation, meniscus sign, achlorhydria, failure to respond to medical treatment.

3. Diaphragmatic hernia: usually best seen in the recumbent and Trendelenburg positions, increase in size with inspiration,[34] usually parallel to superior and inferior surfaces of vertebral bodies, gastric diverticulum usually angulated.[38]

4. Diverticulum in duodenum or jejunum overlying stomach in anterior-posterior view:[46] positioning of patient will distinguish.

5. Elkeles[13] describes in five cases a pouchlike triangular (apex down) shadow on the lesser curvature at the cardia in gastric cancer and likens this to gastric diverticulum. In carcinoma the pouches enlarge progressively with advance of the disease.

6. Tracey[51] points out that rests of barium may be confusing when they float on fluid in a stomach not carefully aspirated before examination.

The importance of using multiple positions in examining the patient is emphasized by the finding of a posterior protrusion at the highest portion of the cardia on the greater curvature in a patient believed, from x-rays taken during life, to have an anterior, lesser curvature diverticulum.[39]

Gastroscopic Appearance.—Schindler observed three instances of congenital diverticulum in 1000 consecutive gastroscopies.[42, 43] These were in the cardia and were described as others have described them[8, 34, 45, 55] as a circular hole lying in normal mucosa without infiltration and separated from it by sharply defined margins. The opening was usually smaller than the diameter of the sac which was lined with smooth orange-red mucosa with normal rugae. The interior of the diverticulum may be rendered visible by ballooning the stomach with air.[55]

Gastroscopy, because of blind spots, may give little information in the typical case of diverticulum at the cardia. Here also there is the greatest danger of perforation with the scope,[51] although in experienced hands this danger is slight. The advantages of gastroscopic visualization are several. Whitehouse and MacMillan[55] believe that gastroscopy should be used in all cases with diverticula in the lower two-thirds of the stomach, as it is in this region that gastric malignancy and penetrating ulcer most frequently simulate diverticulum. Penetrating gastric ulcer usually has a base covered with gray or white exudate or more rarely with blood; the surrounding mucous membrane is quite apt to show evidence of associated inflammatory reaction. Penetrating carcinoma with ulceration may have a nodular base and irregular and infiltrated margins. Gastroscopy also aids in the location of bleeding sites in the stomach and allows the visualization of other gastric lesions prior to surgery.[55]

Complications and Associated Disease, Particularly Malignant Disease.—Inflammation and chronic gastritis may be found in removed diverticula, and bleeding or even massive hemorrhage may result from mucosal erosions.[8] One case is reported[52] in which an inflamed diverticulum lay in a mesh of blood vessels which gave rise to bleeding manifested as hematemesis.

Tracey[61] in thirty-five cases found associated duodenal ulcer in seven cases, carcinoma of the stomach in three, cholelithiasis in two, and diverticulosis of the colon in two. Associated disease of this sort is present in about one-third of the cases, but Rivers and his associates[41] record six cases of apparent gastric diverticulum, four of which had on operation false sacs due to malignant disease or perforating ulcer.

Diverticula have been found to contain in their walls: adenomas, myomas, leiomyosarcoma, fibrosarcoma, lymphosarcoma, carcinoma and precancerous lesions. Martin[20] in 103 collected cases plus twenty-two of his own, cites four references to adenomyoma, one to fibrosarcoma and three to carcinoma, yet he did not believe prophylactic removal was advisable.

Cleve[11] concluded that his lesion (reported under the title of myoma) was a sarcoma, probably developing in a congenital diverticulum in a man of 61. Others have felt that diverticulum-like sacs may arise from degeneration of a preexisting myoma.[23]

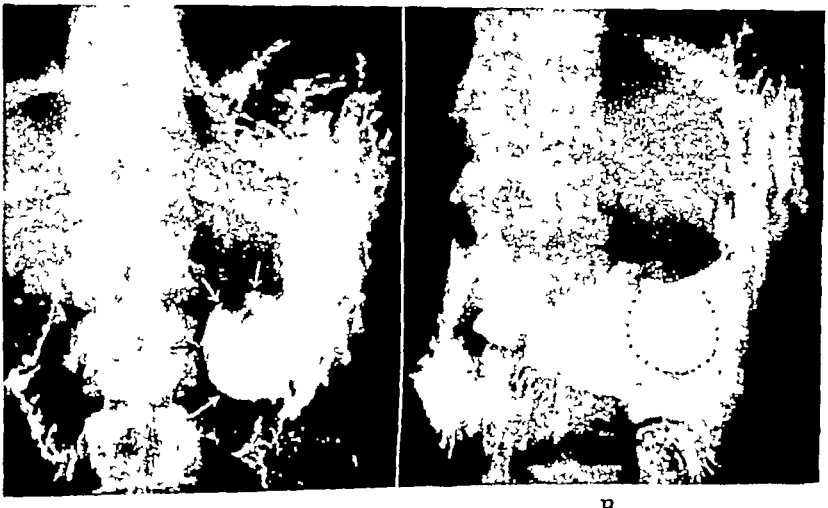
Mellon and his co-workers[28] report precancerous lesions in the gastric diverticulum of a 29 year old man with Boas-Oppler bacilli and erythrocytes in gastric washings. X-ray showed a T-shaped evagination of the greater curvature at the junction of the pars cardia and pars media. Because of weight loss the diverticulum was excised; microscopic study of its wall showed superficial round cell infiltration suggesting that seen in transition areas of the carcinoma of the sigmoid reported. These authors believe that in a mucosal hernia, as it exists

from the remainder of the stomach by pressure, although this was not too well demonstrated in the films taken" (Fig. 71). The stools were dark brown in color and gave a positive test for blood. X-ray of the chest and routine laboratory tests were normal. The patient had lost weight from 160 to 135 pounds within two months; on June 23, 1947 the patient was admitted to Letterman General Hospital.

The past history was not contributory, the patient's habits were moderate, and his family history revealed no taint of malignancy or hereditary disease.

Physical examination showed a thin afebrile young man who had recently lost weight. The blood pressure and pulse rate were normal. A few small lymph nodes were palpable in the postcervical areas, no enlarged Virchow's node was noted. The rest of the physical findings were not remarkable except for a fullness and vague tenderness in the left upper quadrant of the abdomen. A proctoscopy was negative to 22 cm. but the rectum contained dark fecal material thought to contain blood.

A hemogram revealed 4,140,000 erythrocytes and 7850 leukocytes per cu. mm. with normal differential count, and 12.5 gm. of hemoglobin per 100 cc. of blood.



A B

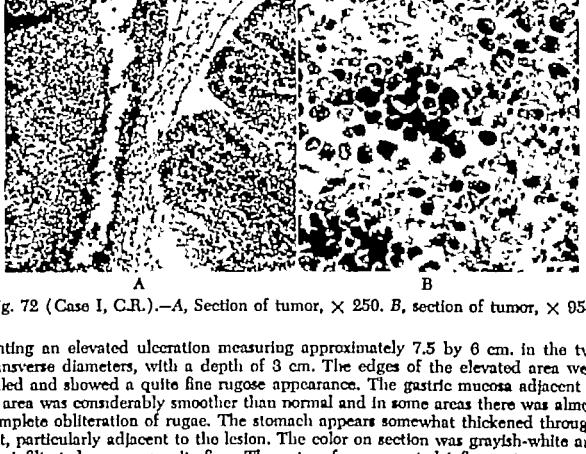
Fig. 71 (Case I, C.R.).—*A*, Barium meal showing huge prepyloric "diverticulum," indicated by arrows. *B*, Barium meal showing huge prepyloric "diverticulum," indicated by dotted line. Barium-filled diverticulum superimposes its shadow on that of the stomach.

Sedimentation rate was 32 mm. in one hour corrected (Wintrobe), the hematocrit 40 per cent. The urine was normal, the stool contained no blood. A gastric tube removed material with free acid of 20 degrees, total acid of 60 degrees, and a positive test for blood. Gastroscopy proved unsuccessful, but one week later, with the patient under cocaine anesthesia, a Cameron gastroscope was successfully passed by the authors. No diverticulum could be made out in the area indicated by *x-ray*, but a pale accumulation of mucosa could be seen in this area; no ulceration or evidence of malignancy could be definitely observed, but the impression was gained of a mass extrinsic to the stomach which made ordinary visability impossible.

In view of the short history, weight loss and anemia, coupled with the suggestive gastroscopic findings, a provisional diagnosis of malignant disease of the stomach was entertained and abdominal laparotomy was advised and performed under continuous spinal and pentothal anesthesia on July 3, 1947. Exploration of the upper abdomen revealed *many large soft succulent nodes scattered throughout the*

gastrohepatic, gastrocolic and transverse mesocolon, and the retroperitoneal area adjacent to the aorta. A large mass was palpable on the posterior stomach wall in the midfundus region. This mass which measured about 6 cm in diameter was found to have perforated into the pancreas and a portion of the greater curvature and posterior wall subadjacent was intimately adherent to the pancreatic tissue. Biopsy of a node showed only an inflammatory reaction. A gastrotomy was performed parallel to the greater curvature of the stomach and immediately overlying this posterior mass so that a better inspection could be made. This revealed a huge crater measuring about 6.5 cm. in diameter and 3.5 cm. deep with gently sloping walls ending in a relatively soft hyperemic and necrotic base. The edges of this mass were gently rolled over and undermined. It was believed to be a large gastric ulcer. A resection was therefore carried out removing about two-thirds of the stomach. A short loop retrocolic terminolateral gastrojejunostomy was accomplished using the full length of the stomach.

The pathological description of the specimen stated that approximately one-half of the mucosal surface had a fairly normal rugose appearance, the other half pre-



A B

Fig. 72 (Case I, C.R.).—*A*, Section of tumor, × 250. *B*, section of tumor, × 950.

senting an elevated ulceration measuring approximately 7.5 by 6 cm. in the two transverse diameters, with a depth of 3 cm. The edges of the elevated area were rolled and showed a quite fine rugose appearance. The gastric mucosa adjacent to th area was considerably smoother than normal and in some areas there was almost complete obliteration of rugae. The stomach appears somewhat thickened throughout, particularly adjacent to the lesion. The color on section was grayish-white and the infiltrated area was quite firm. The cut surface suggested inflammatory process rather than tumor.

Microscopic examination showed hyperplasia of lymphoid follicles, focal collections of lymphocytes and plasma cells in the submucosa and base of the mucosa, as well as in the mucosa itself (Fig. 72, *A*). A submucosal lymphatic was seen to contain cells very similar to those seen in the tumor proper. A large, nodular, fairly well circumscribed tumor mass extended beneath the rolled-up edge of gastric mucosa and was demarcated at this point from another similar mass. The tumor itself was made up of large individual cells (Fig. 72, *B*) showing no pattern and in

most instances lying discrete one from the other. These cells were quite variable in shape, in some instances being round, in others oval, and in still others polyhedral. The cytoplasm was scanty but could be seen; the nuclei were vesicular and showed numerous mitotic figures, occasional prominent nucleoli, and some condensation of chromatin which did not appear to be limited to the nuclear membrane. Reticulum stain revealed no significant reticulum. The tumor did not meet the restricted criteria for reticulum cell sarcoma laid down by Warren and Picena,[54] in that adjacent cells were fairly well separated from each other. Sections of three lymph nodes from the greater curvature of the stomach showed follicular hyperplasia but no invasion by tumor.

It was felt that the tumor was a malignant lymphoblastoma of undetermined cell type. The Army Institute of Pathology made a diagnosis of lymphosarcoma.

Following operation, the patient recovered without incident other than a mild vasomotor reaction which developed while he was receiving a 6 per cent solution of amino acids by vein. In July the blood contained 11.9 gm. of hemoglobin per 100 cc., and 11,400 leukocytes per cu. mm. with a normal differential count. The stool contained no blood.

On July 15 the patient was started on a course of x-ray treatments directed to the upper abdomen in daily doses of 12 r which were increased to 200 r daily and continued until a total dose of 1450 r in air had been given to the anterior field, and 1650 r in air to the posterior field (a tumor dose of 1102 r anteriorly and 1255 r posteriorly). The patient's appetite was poor prior to and during irradiation, and he continued to lose weight. On August 15, at the completion of the x-ray treatment, the patient felt fairly well and his weight was constant despite poor appetite. He was given a thirty day furlough during which he gained about 10 pounds. He had noted a tendency to vomit when eating more than his meager appetite allowed; no blood was noted in the vomitus. The bowels had moved daily and the stools were normal. Occasional fleeting sharp pains had been noticed in the left upper quadrant of the abdomen. The patient complained of occasional "nervous spells" which consisted of instability of the knees, sweating and dizziness, as well as a mild generalized pruritus without external manifestation. The abdominal wound had continued to drain since the time of operation. Physical examination showed fair color, small nonfixed submaxillary lymph nodes, a draining indurated tender abdominal wound, and nothing else abnormal. A hemogram revealed 13.6 gm. hemoglobin per 100 cc., and an eosinophilia ranging from 34 per cent of 6700 to 22 per cent of 9700 leukocytes per cu. mm. on two counts ten days apart. A gastrointestinal series on September 23 showed a normally functioning stoma with no evidence of ulceration. Chest x-ray revealed no evidence of metastasis. The stools contained no occult blood.

As it was felt that the patient had obtained the maximum hospital improvement he was given a Certificate of Disability, and was discharged from the hospital on October 20, 1947. It is felt that his prognosis is hopeless.

Diagnosis: Lymphoblastoma, cell type not determined, of stomach, with direct extension to pancreas.

Comment.—This is a case in which a rapidly growing lymphoblastoma imitated the roentgenologic appearance of a huge diverticulum in the prepyloric area. The clinical history and suggestive findings at gastroscopy led to a laparotomy which revealed an inoperable tumor.

CASE II.—A 45 year old white married woman (St. Luke's Hospital No. E 38665) consulted her physician in April 1946 because of vague indigestion and left upper quadrant abdominal pain. History was difficult to obtain accurately, but indicated that the patient had noted constipation and moderate gastrointestinal upsets asso-

ciated with generalized abdominal cramps and gas. Such upsets often followed indiscretions in diet and were relieved by vomiting. In recent years, but without definite onset, left upper quadrant crampy pain had appeared at and under the left rib margin anteriorly with radiation to the loin but not to the shoulder or elsewhere. This pain had been rather constant since March 1946, was apparently independent of meals and indiscretion, and tended to be better when the patient was lying down. It bore no fixed relation to food, antacids or position, and often interfered with sleep. Examination at the time of an attack showed only local tenderness. The pain was not associated with increase in the other nonspecific symptoms. The patient was afebrile and had lost no weight although she felt increasingly nervous. In May 1946 x-rays of the chest showed no evidence of disease. A gastrointestinal series on May 10 (Fig. 73) showed a large "diverticulum" about

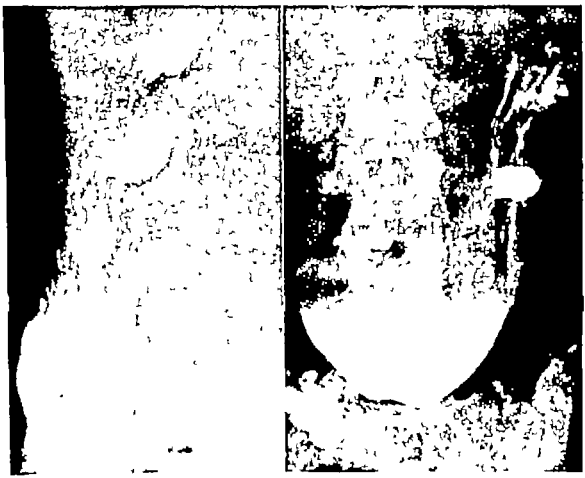


Fig. 73 (Case II, R.L.).—Barium meal showing large midgastric "diverticulum."

2 by 2.5 cm on the posterior surface of the stomach in the proximal half, as well as pylorospasm, multiple diverticula of the descending colon, and "colon irritability." Cholecystograms and examinations of the blood, urine and gastric contents were normal. A fasting gastric content contained 35 degrees of free acid, and 50 degrees of total acid.

The gastrointestinal x-rays were unchanged on June 23 and in August of the same year when the patient again entered the hospital because of increasing pain. The stools with benzidine gave a 3 plus reaction on May 15, 3 plus on June 5, and a negative test on August 2 when the patient had been on a meat-free diet. The urine and Massini and Kolmer serological tests were normal. Hemograms showed 12.5 gm. of hemoglobin per 100 cc., 3.95 million erythrocytes, and 14,400 leukocytes per cu. mm. (81 per cent polymorphonuclear neutrophils). Intravenous pyelograms were normal. The serum amylase was found to be 65 units.

The past history included an episode of cystitis for which the patient had been

twice cystoscoped fifteen years before. Bilateral mastectomies had been performed beginning apparently with removal of a cyst from the right breast in 1919, removal of the breast except for the nipple in 1933, and removal of the nipple in 1939 when the pathological diagnosis was intraductal papillary adenocarcinoma of the nipple, low grade malignancy. A simple mastectomy was performed on the left about 1939, the specimen was reported as "cystic involution of breast." In December 1945 a nodule excised from the scar was reported malignant. Chest x-rays were normal. A fibroid uterus and the left tube were removed in 1937. There were no other significant illnesses, and there was no family history of malignant or hereditary disease.

Physical examination in August 1946 found the patient thin and gray-haired. The glands of the neck were not enlarged, no Virchow's node was found. Both breasts had been removed and there was nothing to suggest a recurrence of malignancy. The lungs were clear except for coarse rales over the left lower lobe; the heart and blood pressure were normal. The abdomen bore a lower midline scar and was pigmented from the application of heat. There was definite tenderness on deep pressure in the left upper quadrant and with firm percussion in the left loin but no masses or tenderness could be made out. The liver edge could be felt 2 fingerbreadths below the right costal margin and seemed normal. Pelvis and rectum were reported normal.

A gastroscopy, done on August 4, 1946, gave an excellent view of the angle and pyloric antrum of the stomach. The mucosa appeared normal and the peristaltic waves were normally active. The duodenal mucosa pouted back somewhat as the waves reached the pylorus. In the upper part of the stomach, about half way between the angle and the cardia, we could see what appeared to be the opening into a diverticulum. The mucosa surrounding this area was slightly redder than the rest of the gastric mucous membrane. Mucosal folds ran over the edge of the opening and appeared to be normal as far as we could see them. There did not seem to be any fixation in this area. We could not see into the depths of the diverticulum. *Diagnosis:* stomach diverticulum.

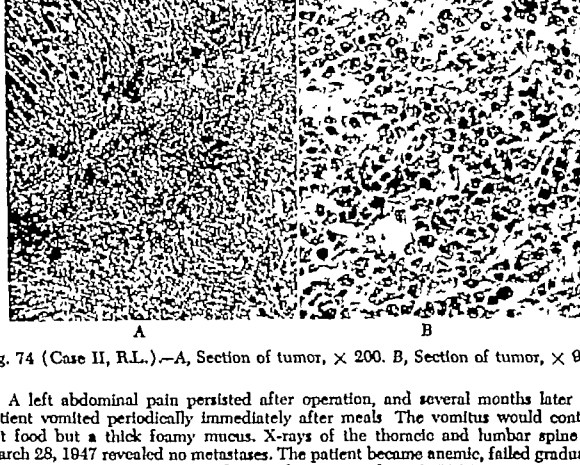
On November 10, 1946 the patient stated that pain was present only when she was tired or excited. A gastrointestinal series showed "small diverticulum near the midportion of the stomach—appeared unchanged. No evidence of new growth in this region." About the first of December the patient first noted sharp left upper quadrant pains unassociated with meals, excitement or fatigue and constant in lesser intensity between attacks. Nausea and vomiting might accompany these episodes, and the pain might be brought on by straining at stool. The patient had lost 5 pounds in nine months. The stool contained occult blood.

Abdominal laparotomy on December 30, 1946 revealed a large elliptical defect in the posterior wall of the stomach extending from above to the left downward and slightly to the right. After opening the stomach this was thought to be a penetrating ulcer about 7 cm. in length by 4 to 5 cm. in breadth lying in the posterior wall of the stomach and penetrating beyond it until its base was adherent to the pancreas. A frozen section of the ulcer edge was reported as "chronic ulcer," although examination of the retroperitoneal area revealed a hard, nodular, indurated mass about 15 cm. in diameter involving practically all of the retroperitoneal tissues. About one-half of the stomach was removed and the remainder was sewed end to end to the pylorus.

Pathological examination of the specimen disclosed, on the posterior wall of the stomach, a large defect bordered by a firm tissue suggestive of the border of an ulcer with steep borders and a firm base. In at least one area, however, there was a firm white tumor consistent with carcinoma. This appeared to be in the border of the ulcer rather than at the base, and extended for a maximum distance of 10 mm. from the surface of the ulcer into the adjacent gastric wall. The lesion involved the posterior wall of the stomach, and lay somewhat more toward the greater than

toward the lesser curvature. The gastric wall at a distance greater than 1 cm. from the ulcer border appeared normal. No enlarged lymph nodes were demonstrated.

Microscopic examination showed extensive, very cellular carcinoma characterized by the presence of relatively small cells exhibiting hyperchromatic nuclei and a few mitotic figures (Fig. 74). The diagnosis was reported as adenocarcinoma of stomach, grade III.



A B

Fig. 74 (Case II, R.L.).—A, Section of tumor, × 200. B, Section of tumor, × 950.

A left abdominal pain persisted after operation, and several months later the patient vomited periodically immediately after meals. The vomitus would contain not food but a thick foamy mucus. X-rays of the thoracic and lumbar spine on March 28, 1947 revealed no metastases. The patient became anemic, failed gradually despite supportive measures, and expired on September 20, 1947. An autopsy was not done.

Comment.—This patient illustrates the difficulties in diagnosis of carcinoma of the upper end of the stomach which have been so well emphasized by recent authors.[23, 53] In this case proper diagnosis was delayed not only because of the absence of symptoms of a conclusive nature, but also because the "diverticulum" observed on repeated x-ray examinations failed to change. Gastroscopy, while it revealed the area in question, was actually misleading in its information. The position of the protrusion, in the lower two-thirds of the stomach, remained as the only clue which might have definitely indicated earlier operation.

REMARKS

Diverticula of the stomach present few definitive clinical symptoms to aid in their recognition. Pain, vomiting and belching which sometimes herald their presence are most often due to other disease. Diagnosis by x-ray of the stomach is upon firmer ground (vide supra)

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THE DIAGNOSIS AND TREATMENT OF THE COMMON FORMS OF STOMATITIS

GARNETT CHENEY, M D *

MOST diseases of the mouth are due to some form of inflammation, the cause of which is often obscure The affected area may be limited to a single structure such as the gums or extend to all the structures of the oral cavity, including the tongue. Whether the stomatitis is localized or generalized, an exact etiologic diagnosis should be determined, and a specific form of treatment should be carried out. In view of these facts it is desirable to attempt to classify the various forms of stomatitis on an etiologic basis rather than on the basis of the anatomic location of the lesions, or according to the appearance of a given pathologic process, as has so often been done in the past. To state that stomatitis is catarrhal, aphthous, vesicular, bullous, ulcerative, ulceromembranous or gangrenous tells nothing as to the true nature of the disease affecting the mouth, and is all too reminiscent of the dermatologist's descriptive diagnoses of many diseases of the skin

A number of factors have led to a renewed interest in oral disorders and have emphasized the need for a better understanding of their causes and their management. In addition to the various fractions of vitamin B complex which may cure certain lesions of the lips, gums, buccal mucosa, palate and tongue, it has recently been shown that folic acid will cure similar lesions, such as those which occur in sprue and in pernicious anemia The tremendous interest in the scope of penicillin therapy has already extended to ulcerative stomatitis Cases of unknown cause have been clearly benefited. The use of streptomycin is on trial in similar cases Extensive modern studies of diseases transmuted by a virus have enhanced our knowledge of herpetiform lesions and developed the virus disease concept of Steven-Johnson's syndrome The newly described disorder of splenic neutropenia has stimulated further interest in the relationship of granulocytopenia to canker sores in the mouth Although most oral affections are not disabling, they are extremely uncomfortable and irritating so that more efficient methods of diagnosis which lead to more efficacious forms of treatment will be most welcome to patients suffering from stomatitis

Classification of Stomatitis Based on Etiology.—Although the exact cause of many cases of stomatitis cannot be accurately deter

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mined, the number of cases of obscure origin is diminishing. In an attempt to classify diseases of the oral cavity primarily on a basis of etiology, it is well recognized that in many instances the underlying cause of the clinical manifestations can only be assumed. This is particularly true of disorders caused by virus infections. However, there are many known etiologic agents which cause the various forms of stomatitis and which can serve as a firm groundwork for the erection of an enduring classification of oral disease.

Physical or traumatic causes such as tartar deposits on the teeth, carious broken teeth, rough crowns, ill-fitting plates and fractured dentures; excessive heat; toxic chemical substances; electrical reactions (electrogalvanic lesions); local toxic reactions to systemic diseases such as septic infections and typhoid fever and the gingival deposits of heavy metals which have been used therapeutically may all cause inflammation of the oral mucous membranes. Bacterial infections which must be considered as a cause of stomatitis are diphtheria, streptococcal infections, the fusiform bacillus and spirillum of Vincent's stomatitis and the Treponema pallidum of syphilis. Rare bacterial causes are the pneumococcus and the tubercle bacillus. Oral lesions of virus etiology occur in herpetiform stomatitis, foot and mouth disease and possibly in Steven-Johnson's syndrome. Fungous infections of the mouth are common in poorly nourished infants and in the debilitated aged, but are relatively rare in adult medical practice.

Deficiency disease is a most important cause of stomatitis and glossitis. The clinical disorders commonly associated with vitamin deficiency disease which leads to stomatitis are beriberi, pellagra, pernicious anemia, sprue, scurvy and vitamin M (folic acid) deficiency, but any prolonged dietary deficiency or persistent diarrhea may lead to a similar result. An allergic cause of stomatitis, particularly aphthous stomatitis, must always be kept in mind. Neutropenia, whatever its progenitor, frequently leads to a severe form of stomatitis. Finally chronic irritation of the oral mucous membranes leading to the development of leukoplakia must be recognized as a potential cause of cancer.

Traumatic, Thermal and Chemical Causes of Stomatitis.—The diagnosis of the various forms of traumatic stomatitis rests largely on a careful dental inspection of the gums and teeth and x-ray studies in selected cases. The inflammation usually occurs as a gingivitis secondary to caries, tartar deposits and poor oral hygiene. Pyorrheal infection advances, leading to peridontoclasia and abscess formation at the apices of the teeth. If periodontoclasia is not advanced, the gingivitis may be arrested by good dental care, scrupulous oral hygiene and mechanical stimulation of the gums three times daily with a stiff-bristled tooth brush. The use of an alkaline mouth wash such as liquor aromaticus alkalinus, N.F., morning and night will promote healing. If areas of localized inflammation are due to physical condi-

tions, such as rough crowns, poorly fitting bridges or improper dental plates, these causative factors must be removed.

Inflammation of the mouth and tongue due to hot food or liquids or to the swallowing of chemical substances such as strong acid or alkali solutions, lysol or bichloride of mercury, can only be accurately diagnosed by a careful history. The location and degree of inflammation will vary with the amount of the injurious agent and the rapidity with which it was ingested. In treating this form of stomatitis, a soft, nonirritating form of diet should be ordered. Alcoholic beverages and smoking should be forbidden. A cleansing, soothing mouth wash such as 12 per cent borax in a 10 per cent solution of glycerine, or a 50 per cent solution of hydrogen peroxide, U.S.P., should be used four times daily. In the more severe cases warm saline or sodium perborate irrigations should be used every four hours.

Stomatitis medicamentosa may follow the use of mercury, bismuth and, less commonly, gold therapy. The gums are primarily affected and may become acutely inflamed. They may bleed and become ulcerated and in severe cases the teeth often become loosened. Bismuth deposits are seen as slate gray flecks in the gingiva, not unlike a "lead line." Lead deposits do not commonly cause gingivitis. The administration of the water-soluble preparations of bismuth is much more likely to produce a severe gingivitis. The diagnosis of stomatitis medicamentosa is usually evident from the history. The inflammation tends to cease promptly after withdrawal of the causative drug. Symptomatic therapy of the stomatitis is temporarily indicated. The probability that this form of oral inflammation is more likely to occur in a debilitated vitamin deficient individual must be considered, and suitable vitamin therapy started early if there is the slightest indication for its use. Vitamin B complex and vitamin C in therapeutic doses orally are ordinarily sufficient.

Stomatitis Caused by Bacterial Infections.—Inflammation of the oral cavity caused by bacteria may be localized to the gingiva or soft palate and pharynx, or involve all structures in the form of a diffuse stomatitis. Erythema, various types of ulceration and membrane formation may occur singly or in combination. Certain routine diagnostic procedures should be utilized as in other types of infection. Of particular importance are smears and bacterial cultures from the affected areas, and white blood cell counts. In febrile cases a graphic temperature chart of the rectal temperatures should be recorded.

Hemolytic streptococcus infection occurs in two forms. In the first form it complicates pyorrhea which leads to periodontoclasia and dental abscesses, and may in rare instances act as a focus of infection for systemic disorders. In the second form the infection is primarily in the tonsils and pharynx and spreads anteriorly to the soft palate and to the buccal mucosa, often producing marked erythema and edema. Anterior cervical adenitis is the rule and fever and leukocytosis fre-

quently occur. An accurate diagnosis of both forms depends on culturing a heavy growth of the streptococcus from the gums or throat. The mere presence of hemolytic streptococcus organisms does not necessarily prove they are the cause of the symptoms. Treatment of the gingival involvement is usually the same as that of periodontoclasia, and may include extraction of infected teeth. It is not likely that penicillin given either locally or by parenteral injection will clear up this type of infection, but it may be used as an adjunct to dental therapy.

Whether or not sulfadiazine or penicillin therapy will definitely clear up hemolytic streptococcus infections of the posterior buccal cavity is still a moot question. The treatment of choice is intramuscular injections of either 50,000 units of sodium penicillin every four hours for five to seven days, or of 300,000 units in beeswax and oil daily for the same period of time. Improvement should occur in twenty-four to forty-eight hours. Salicylates or codeine may be given for pain. Local treatment for inflammation should be carried out in the same manner as described for the management of stomatitis due to chemical causes.

Dipththeria bacillus infection occurs in the posterior buccal cavity and throat in a manner similar to hemolytic streptococcus infection except that membrane formation is much more likely to develop. Throat cultures are indispensable for a positive diagnosis. The treatment is the administration of diphtheria antitoxin. The amount of antitoxin given must be in proportion to the severity of the infection. The dose will vary between 5000 and 100,000 units. Additional therapy is similar to that given for streptococcus infections.

Vincent's stomatitis, or trench mouth, said to be due to fusiform bacillus and spirillum infection, is a disorder which at the present time is difficult to evaluate as a disease entity. Simple cases of gingivitis in which a few organisms of Vincent are found are often erroneously diagnosed trench mouth by both physicians and dentists. If there are ulceromembranous lesions of the gingiva and buccal mucosa, which smears show to be teeming with Vincent's organisms, a diagnosis of Vincent's stomatitis is justified, although it is not certain whether these organisms are primary and causative or secondary invaders. Parenteral penicillin therapy as recommended for oral streptococcus infections is usually rapidly curative. The beneficial effect of 5000 unit penicillin lozenges dissolved in the mouth hourly while the patient is awake is remarkable in certain cases and their use is well worth a trial in the milder cases. Warm saline irrigations and hydrogen peroxide mouth washes promote comfort. Oral pain may be relieved locally by anesthesia-troches, or by the use of codeine orally or by hypodermic injection. Adequate vitamin therapy with vitamin B complex and vitamin C is a sound routine procedure. Some cases clear up on vitamin therapy alone. In differential diagnosis the mouth le-

sions of secondary syphilis, the leukemias, agranulocytosis, pemphigus and virus infections must be kept in mind.

A well recognized bacterial cause of stomatitis is *secondary syphilis* which produces mucous patches of the buccal mucous membranes and may involve the throat in ulcerating lesions. Extraoral signs of syphilis may be lacking. Darkfield examination of material from the mucous patches will disclose the Treponema pallidum, and blood complement-fixation and precipitation tests for syphilis will be positive. An important aspect of diagnosis is constantly to suspect the presence of syphilis when the cause of a persistent stomatitis is not clear. Standard penicillin therapy for secondary syphilis will clear up the mouth lesions rapidly.

Stomatitis Due to Virus Infection.—Vesicular, herpetiform, aphthous and ulcerating lesions of the mouth and tongue may be due to virus infections; however, herpes virus is the only virus which has been identified as commonly causing stomatitis. The virus of foot-and-mouth disease is a much less common cause. A virus may be the cause of Stevens-Johnson syndrome. A virus etiology of many other cases of stomatitis is suspected but is rarely proved. In febrile cases without leukocytosis, which do not respond to penicillin therapy, a virus infection must be considered.

Acute infectious gingivostomatitis or *herpetic stomatitis* due to herpes simplex virus not only occurs in infants and children but also in adults.[1] Its incidence is higher than the current medical literature would suggest. The patient often becomes acutely ill with rapid pulse and high fever. Mouth and throat lesions progress from scattered tiny vesicles with an erythematous halo to profuse coalescing ulcerations which cause severe pain. Oral fetor and cervical lymph gland adenopathy are common. The diagnosis can be confirmed by inoculation of the infected contents of a vesicle into a rabbit's cornea and the demonstration of inclusion bodies in the corneal cells. The diagnosis may be made in retrospect by complement fixation tests of the patient's serum for herpes virus. Specimens of blood are obtained early in the course of the illness and during convalescence. A pronounced rise in antibody titer may be accepted as proof of herpes virus infection. However, this serological test is not generally available. Treatment for the stomatitis is purely symptomatic. Repeated vaccination for smallpox may prevent recurrence.

Stevens-Johnson syndrome is an eruptive fever with involvement of the respiratory tract, conjunctivitis, stomatitis and balanitis.[2] It has also been called erythema exudativum multiforme of Hebra and erythema or herpes iris conjunctivae. Lesions in the oropharynx tend to appear early in the illness and present a difficult problem in diagnosis before the appearance of characteristic lesions elsewhere. A virus etiology has not as yet been positively established. Here again only symptomatic treatment of the stomatitis is clearly indicated. Both

sulfonamide drugs and penicillin may be tried, but have failed to produce definite improvement in the majority of cases.[2, 3]

Foot-and-mouth disease is a known virus infection producing stomatitis but its presence in the United States has not yet been proved. Characteristic vesicles on the hands and feet distinguish it from other types of stomatitis. The presence of the virus in the mucous membrane and skin lesions can be proved by inoculation of infected materials into guinea-pigs.

Stomatitis Caused by a Fungus Infection.—Mycotic stomatitis, or fungus infection of the mouth, occurs in the form of *thrush* which causes patchy white membranous lesions of the gums, buccal mucosa and tongue, and as a localized granulomatous infiltration due to Actinomyces bovis infection. Thrush, or moniliasis of the mouth, is commonly caused by Monilia albicans, but can be caused by a number of different parasites. A diagnosis is readily established by smears from the lesions and cultures of the monilia on Sabouraud's medium. Scrupulous oral hygiene and local treatment with a mouth wash of an aqueous solution of boric acid or of gentian violet is usually curative. In chronic latent oral moniliasis no treatment is effective.[4]

Although early *actinomycosis* produces a purplish discoloration of the gingivae or cheek, the later granulomatous manifestations do not come under the heading of stomatitis. An early diagnosis is based on the characteristic history of chewing grass or hay, and a biopsy of the lesion which shows the sulfur-like granules of the ray fungus or produces a characteristic fungous growth on Sabouraud's medium. Large doses of potassium iodide orally and of penicillin parenterally may clear up an early case.

Stomatitis Due to Deficiency Disease.—Stomatitis with glossitis is common in states of pronounced malnutrition whatever the cause. However, there are certain well recognized deficiency diseases in which they are characteristic findings and in these disorders the oral manifestations can usually be relieved by specific vitamin therapy. They may occur initially and exist for some time before other signs of disease develop and they then present a difficult diagnostic problem. The diagnostic study must include not only a detailed history, careful physical examination and routine tests of the urine and blood, but also estimations of red blood cell size and diameter and blood serum bilirubin content, tests of the blood clotting mechanism, gastric analysis, stool analysis and x-ray examination of the gastrointestinal tract. Once these procedures are completed, the diagnosis of stomatitis and glossitis due to *pernicious anemia, sprue, pellagra, "beriberi," scurvy* or a deficiency state secondary to an *inadequate diet* or *excessive diarrhea* is not difficult. Although the shiny red tongue of an atrophic glossitis is most common early in most of these disorders, a generalized stomatitis frequently develops and may become exten-

sive. Secondary infection of the mouth lesions is not uncommon and complicates the clinical picture.

In treating the stomatitis secondary to a known deficiency disease, liver extract, folic acid, vitamin B complex or vitamin C is all that is required as a rule. In pernicious anemia the mouth and tongue lesions usually clear up rapidly once concentrated liver extract therapy is instituted. Occasionally thiamine hydrochloride or folic acid in doses of 5 mg. orally three times a day must also be given to alleviate the stomatitis. In sprue, folic acid in the same dosage is now known to be specific in relieving the oral manifestations of this disease. Additional therapy with vitamin B complex may be indicated. Stomatitis in pellagra clears up coincident with niacin and riboflavin therapy orally or parenterally, using niacin in 100 mg. doses three times a day and riboflavin in 5 mg. doses three times a day until healing occurs. Vitamin B complex as liver extract, yeast extract, or rice husk extract is a valuable adjunct to treatment as many cases suffer from a multiple vitamin B deficiency. Vitamin B_1 is specific for the treatment of beriberi, but vitamin B complex should also be used in addition to thiamine hydrochloride therapy. The oral lesions of scurvy improve rapidly after vitamin C therapy. A dose of 100 mg. of ascorbic acid three times a day is sufficient. In nonclassifiable deficiency states all types of therapy mentioned should be combined in each case to assure healing of mouth lesions that occur on a nutritional deficiency basis.

Stomatitis Caused by Allergy and by Other Conditions.—Oral manifestations of allergy occur in two forms, *canker sores* and swelling of the lips, soft palate and tongue due to *angioneurotic edema.* The diagnosis may be clear from the patient's history of developing symptoms relative to eating some particular article of food; but more often a complete survey for allergic reactions may be necessary to establish the exact diagnosis. The most satisfactory treatment is elimination of the offending allergens.

It must always be remembered that oral lesions, particularly if hemorrhagic, develop secondarily to leukemia, Hodgkin's disease, purpura and agranulocytosis. The diagnosis of these conditions requires complete clinical studies; and specific therapy for the stomatitis is that of the underlying disease. Various forms of oral lesions occur as mucosal manifestations of a variety of skin diseases. Pemphigus vulgaris, erythema multiforme, lupus erythematosus and lichen planus are worthy of mention. The diagnosis is based on the characteristic skin lesions. Many forms of therapy have been tried, most of which are unsatisfactory. An extremely chronic inflammatory lesion of the mouth is known as *leukoplakia.* It is very important to recognize the tough, white, irregular mucous membrane patches of this disorder, as it is a precancerous condition. A biopsy may be necessary to establish the diagnosis. Radium therapy, electrocoagulation and cautery are all successful forms of curative treatment.

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LESIONS OF THE ESOPHAGUS

Diverticulum, Cardiospasm, Megaesophagus and Cancer

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THE diagnosis of esophageal lesions can be made with accuracy because the interior of the esophagus can be seen through the esophagoscope; obstructions, spasm and diverticula are demonstrable

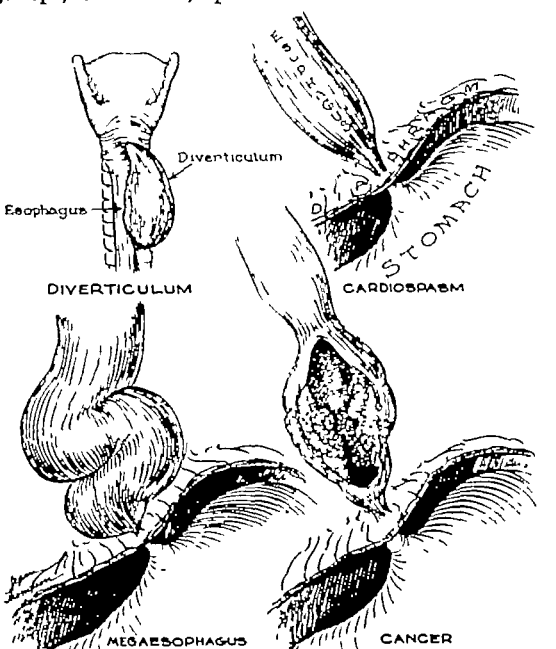

Fig. 75.—Esophageal lesions

with the roentgen ray. Despite these truths, morbid changes of the esophagus are often diagnosed late or not at all. There are several

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reasons for this. The esophagoscope is available only through the medium of relatively few skilled specialists. Most specific esophageal lesions are surgical in nature, and until recently and with a few exceptions, they were difficult and hazardous to approach. Hence, where little could be accomplished in the way of a cure, diagnostic interest tended to lag.

With the development of new surgical technics, the thoracic portion of the esophagus can now be explored with minimal risk, and operations which maintain or restore the direct continuity of the esophageal gastric canal have become established procedures. As a result the interest of the doctor in the esophagus has revived. Fortunately, a correct diagnosis can be made in most cases on the basis of history, physical findings and roentgen ray examinaton. Such facilities are available to all. Surgical treatment is the province of the specialist.

The four esophageal lesions to be discussed are illustrated graphically in Figure 75.

DIVERTICULUM

Diverticula of the esophagus which are most likely to produce symptoms and require surgical removal occur posteriorly at the cricopharyngeal juncture. They are probably developmental but not congenital in origin. The sac consists of herniated mucosa and submucosa without muscular cover except for a few fibers at the base. They commonly develop in men past middle age, apparently as a result of increased pressure from within the esophagus acting on a weak point in the muscular wall, with resulting herniation of the mucous lining of the esophagus. Once formed, the sac tends to enlarge and extends downwards on the left side of the neck and may enter the mediastinum. Diverticula thus will vary in size from those capable of holding a few cubic centimeters of fluid to sacs which may contain several hundred cubic centimeters of liquid and masticated food. Less frequently diverticula form in the intrathoracic portion of the esophagus. Fortunately, these are usually small and do not produce sufficient disturbance to warrant surgical removal except in very rare instances.

Diagnosis.—A man of 60 came to us complaining of dysphagia. On further questioning it developed that after moderate drinking or eating he developed a fullness in the left side of his neck followed by a choking sensation and inability to swallow anything more. His symptoms began three years previously and had grown progressively worse. He obtained temporary relief by regurgitating liquid and undigested food. He discovered he could facilitate this act by pressing on the swelling on the left side of his neck. His family noted a peculiar clicking or clacking sound when he spoke. There was moderate weight loss. A diagnosis of pharyngo-esophageal diverticulum was confirmed by roentgen ray examination. The patient was completely relieved of his symptoms following a one-stage surgical excision of the sac.

This patient presented the typical clinical picture of large pharyngo-esophageal diverticula. Patients with smaller lesions may complain only of occasional difficulty in swallowing. A common symptom is the regurgitation of fluid and undigested food on lying down at night.

The roentgenological finding of a sacular lesion coming from the esophagus confirms the diagnosis.

Treatment.—Small diverticula may be treated by prescribing a smooth nonirritating diet, with instructions to the patient in slow mastication and swallowing. As there is often some narrowing of the esophagus or spasm where the sac originates, relief is afforded by occa-

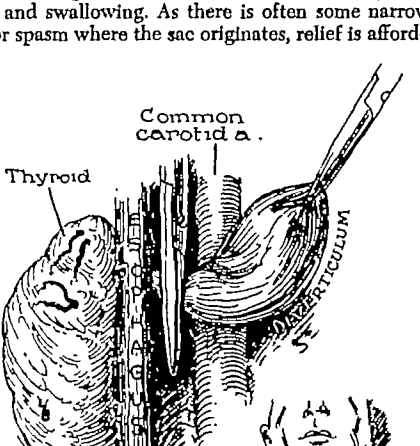

Fig. 76.—Diverticulum showing method of excision.

sional dilatations with metal bougies on a flexible whalebone staff guided over a previously swallowed thread.

When the symptoms and the size of the sac warrant it, surgical extirpation (Fig. 76) of the sac is indicated and results in cure. We now perform the operation in one stage. A transverse incision is made in the neck, which provides adequate exposure and gives a better cosmetic result than the diagonal incision along the border of the sternocleidomastoid muscle still being used in most other clinics. The sac is found and dissected free to where it emerges from the esophagus. A clamp is placed across the neck of the sac taking care not to

infringe on the walls of the esophagus. The sac is cut off and the stump inverted by means of chromic catgut and interrupted silk sutures. Penicillin is given and the patient is fed for a few days through a small soft tube passed into the stomach either prior to or at the time of operation.

CARDIOSPASM

Primary cardiospasm is more frequent than is generally supposed and has long been recognized as a clinical pathologic entity. The obstruction is intermittent at first and results in gradual distention of the esophagus which in advanced cases may be extreme. Recurrent attacks of dysphagia occur in all the patients and substernal pain which may be severe is present in half of the cases.

Nature of Cardiospasm.—Despite a good deal of investigative work the cause of primary cardiospasm is not as yet clearly understood. The spasm or point of narrowing occurs in the esophagus where it passes through the esophageal hiatus of the diaphragm. Above this point the esophagus funnels out smoothly and sharply and may be dilated to three or four or more times its normal diameter. In its narrowed portion the wall of the esophagus is thickened but not rigid and can be readily distended by firm expansile pressure from within its lumen. The musculature above is more or less hypertrophied but shows no other marked changes beyond some evidence of mild inflammatory reaction in advanced cases.

Diagnosis.—The disease occurs most commonly in young adult women but we have seen it in both sexes and at ages varying from 14 to 76 years. Some of the patients are of the nervous high-strung type, but the condition is definitely not a neurosis but a true organic lesion.

Patients who have cardiospasm give a history of periodic spells of difficulty in swallowing lasting over a period of years. Actually they have no difficulty in carrying out the voluntary portion of the act of swallowing but describe ingested food or liquids as sticking or lodging under the lower end of the sternum. In the early stages the spasm is intermittent and there may be long periods of freedom from trouble. In the beginning, liquids, especially cold liquids, often cause more difficulty than solid foods. Gradually the spasms occur with more frequency and finally the patient is unable to take any type of food in comfort.

Patients adopt various procedures to force the food through the spastic area. Some obtain relief by standing and drinking large quantities of fluids, forcing the spasm by means of pressure from above. Others, by closing the glottis, seem to be able to compress the esophagus by means of increased intrathoracic pressure and thus force the food through the constricted area. Still others find it best to eat only

small amounts at a time and, following varying intervals, the spasm temporarily releases itself. All patients at times are forced to regurgitate the contents of the esophagus in order to obtain relief.

In spite of their difficulty in passing food into the stomach, many patients go on for years without any great loss of weight or strength, while others become markedly emaciated and anemic.

Differential Diagnosis.—The condition has to be differentiated from cancer of the esophagus and benign organic stricture. The long history, its intermittency in the early stages, and the characteristic x-ray appearance differentiate cardiospasm from cancer. However, in several of our patients a previous diagnosis of cancer had been made. One such patient had had a gastrostomy performed elsewhere and had been given a fatal prognosis. Our diagnosis was cardiospasm, which was confirmed. The condition was cured by hydrostatic dila-

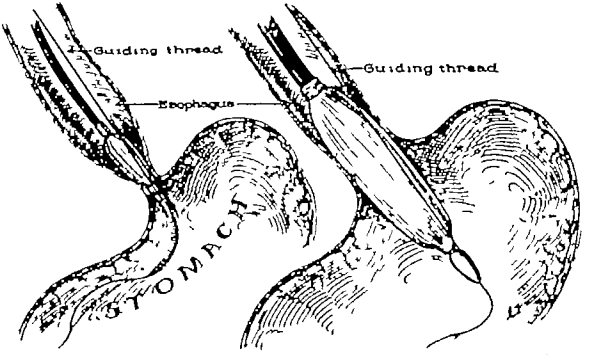

Fig. 77.—Cardiospasm. Method of dilating with bougie and Plummer bag.

tation, and the gastrostomy opening was allowed to close. Organic stricture can be differentiated on the basis of the history and x-ray appearance.

Treatment.—A satisfactory method of treatment has long been known but little practiced except by a few. Our procedure follows that described by Vinson and Moersch and consists of forceful dilatation of the spastic area by passing a No. 45 French olive, following at once with a No. 60 French olive guided over a previously swallowed and anchored silk thread (Fig. 77). If this treatment proves insufficient, it is followed in a week or more by hydrostatic dilatation with a Plummer bag. Most patients are given permanent relief but a few require additional dilatation.

MEGAESOPHAGUS

In cardiospasm the dilated esophagus tapers smoothly and gradually a distance of one to several centimeters to the point of maximum narrowing at the esophageal hiatus in the diaphragm. In these cases the esophagus curves slightly and gracefully to the left towards the cardia (Fig. 75). In a few extreme cases the esophagus is not only greatly dilated but also lengthened and terminates in a reclining S-

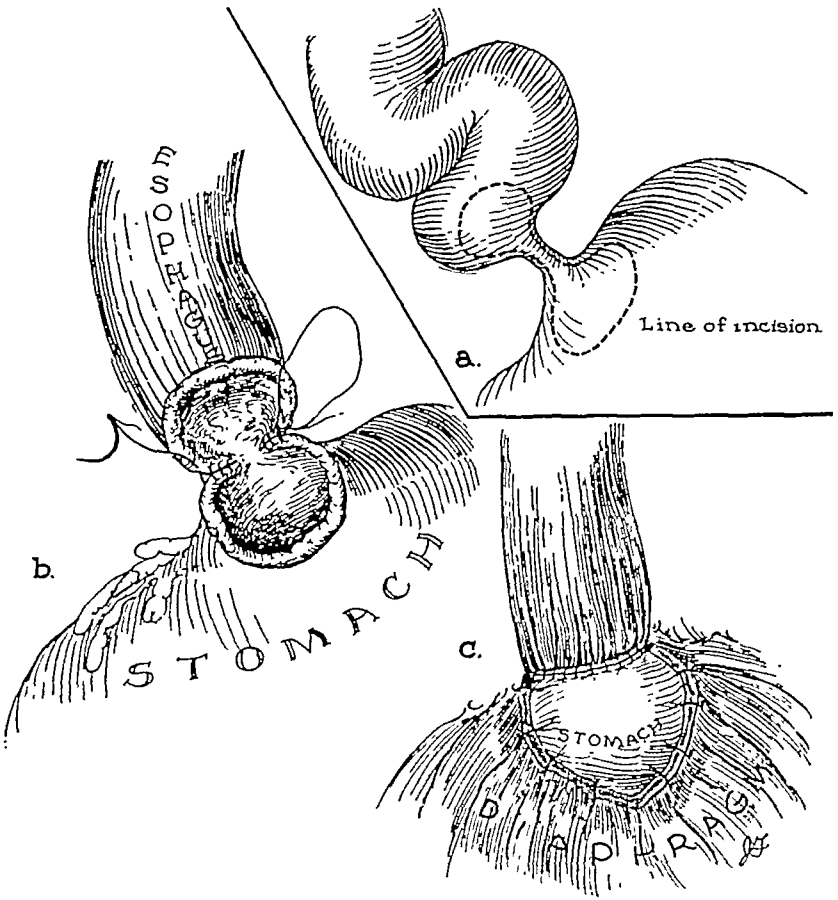

Fig. 78.—Megaesophagus. *a*, Line of excision. *b*, Re-anastomosis. *c*, Finished operation.

shaped curve before the lumen becomes almost obliterated at the esophageal hiatus in the diaphragm (Figs. 75 and 78,*a*).

We prefer the term megaesophagus rather than cardiospasm to describe this latter condition. There are reasons for believing the two lesions are different and that the one is not merely an advanced stage of the other. Megaesophagus has been found in infancy and even in fetal life. Treatment by dilatation incurs greater risk in these patients

and in some it cannot be done because of the angulation of the lower esophagus.

While operating on several of these patients, we have observed that the point of maximum narrowing is at the esophageal hiatus in the diaphragm, as it is in cardiospasm. The wall of the esophagus at this point is thickened but does not bulge outward and is not fibrosed. The opening in the diaphragm is smaller than normal and the musculature of the diaphragm surrounding the opening is abnormally thick and hypertrophied. It would seem quite possible that in these cases the primary lesion does not lie in the esophagus but is due rather to a congenitally small hiatus and may be further aggravated by hypertrophy of the surrounding diaphragmatic muscle with sphincter-like action compressing the esophagus.

Symptoms.—Recently a woman in her twenties was brought to the hospital by ambulance. She looked like the victim of a concentration camp or famine in India. She was indeed slowly starving to death by reason of a marked idiopathic narrowing of the lower esophagus Above this her esophagus was tortuous and greatly dilated.

After adequate preparation with intravenous fluids and blood transfusions, the patient was operated upon by the transthoracic approach. The diaphragm was opened with a short incision extending through the thickened muscle of the esophageal hiatus. A partial excision of the narrowed esophagus was done and the opening thus made was reunited as an esophagogastrostomy (Fig. 78). The patient recovered without complication and is now eating normally and has gained 40 pounds in weight. She had always had some difficulty in assimilating food and it seems entirely possible she was born with a narrow esophageal hiatius, the constriction later becoming more marked as a result of muscular hypertrophy about the opening.

Symptomatically, patients with megaesophagus behave the same as patients with a severe grade of cardiospasm. At first the obstruction is intermittent and incomplete, but in the later stages it becomes constant and nearly total.

Treatment.—An important reason for differentiating between cardiospasm and megaesophagus is that in the former the proper treatment is always forceful dilatation, while some of the latter patients require surgical correction. With the better results and decreased hazard of operation resulting from improved surgical technics, anesthesia and employment of antibiotic agents, an increasing number of patients are being operated upon. It is likely under these circumstances that the operation will be overdone. It should be emphasized that only the very occasional case needs surgical correction. The vast majority of patients will respond to treatment by dilatation.

CANCER

Cancer of the esophagus occurs with unwonted frequency. Physicians have too often witnessed the tragic picture of some one slowly starving to death with this dread disease, made worse in the knowledge that nothing can be offered to cure or even greatly relieve their suffering.

Recent developments have somewhat brightened this dark picture and it is now possible to resect lesions of the intrathoracic portion of the esophagus and restore the normal continuity of the gastrointestinal tract. This should make us redouble our efforts to detect esophageal cancer in its early stages.

Symptoms.—No new methods of diagnosis can be presented, but the presence of cancer should always be considered a possibility when dysphagia is complained of, especially in patients over 40 years of age. More frequent use of the esophagoscope is indicated but unfortunately is not practicable because of the limited number of specialists who are able to use this instrument. In most instances we must rely on the roentgenologist for the detection of early cancerous growths in the esophagus.

Dysphagia and loss of weight are the most common symptoms. Pain is inconstant, at least as an early symptom, and is often an indication of extension of the growth beyond the walls of the esophagus. This, however, should not preclude surgical exploration because we have been able to free some growths which at first seemed quite fixed. As is true in cancer elsewhere, at least a part of the fixation may be due to an accompanying inflammatory reaction.

In our clinic esophagoscopy is done in all patients suspected of having cancer of the esophagus. Unfortunately, however, it is not always an infallible aid in arriving at the correct diagnosis. Even when an obstructing growth can be seen and a biopsy taken, at times the biopsy may show only inflammatory tissue, when actually there is a cancer present. In such cases the specimen has been taken too near the periphery. This is difficult to avoid, as the constriction beginning above the growth often prevents passage of the esophagoscope to the actual level of the growth. Formerly we were loathe to operate in the absence of a positive diagnosis. More recently, because of the very slight risk involved in opening the thoracic cavity, we have not hesitated to explore in the absence of pathological confirmation of the diagnosis of cancer where the symptoms and other findings strongly suggested the presence of such a lesion. This is not inconsistent in view of the further fact that certain benign lesions in this location also at times require surgical correction.

One of our patients suspected of having an early carcinoma proved to have an inflammatory stricture of unknown origin. She was completely relieved of her symptoms by freeing the esophagus from its attachments in the neighborhood of the stricture.

Even the patients who were found to have inoperable growths were considerably relieved of their obstructive symptoms by freeing the growth from the surrounding tissues. Some improvement in the obstruction has occurred in all of our patients whose growths were not resectable. One of our patients, whose esophagus had been almost totally obstructed prior to surgical exploration, after the growth was partially freed was able to take soft foods as well as liquids quite

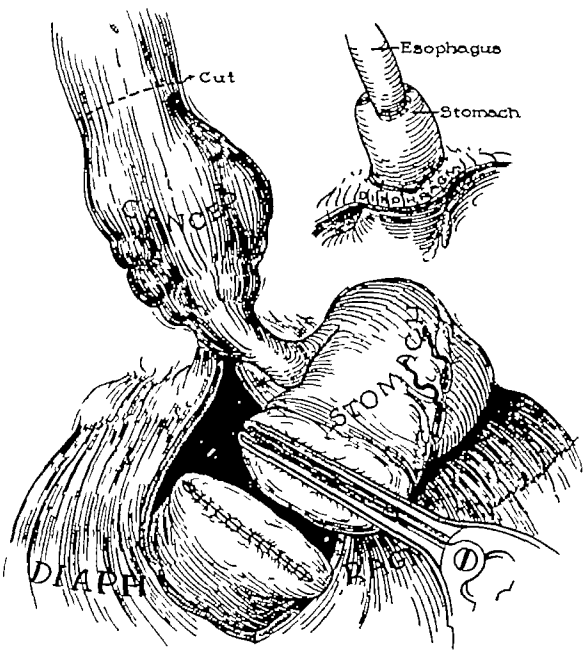

Fig. 79.—Cancer. Illustrating method of excision and anastomosis.

freely until exitus six months later. This has led us to free the growth so far as possible even in those cases which are seen to be inoperable as soon as the thoracic cavity is opened.

Patients with carcinoma of the esophagus who are not explored because of obvious inoperability are best treated by dilatation with bougies over a previously swallowed thread. Even when the obstruction seems almost complete, the thread will pass, and such patients

can frequently be given some slight if only temporary relief from their most distressing symptom. We very rarely perform gastrostomy or jejunostomy as a palliative operation.

Treatment.—The patients are usually elderly and in varying stages of starvation, making adequate preoperative preparation an essential for success. Preparation for surgery consists of hydration of the patient with intravenous gluocse and saline until a satisfactory urinary output is attained. Blood transfusions and amigen are given to correct anemia or hypoproteinemia. The esophagus above the obstructed point is thoroughly cleansed by means of a Levin tube and suction. Penicillin and streptomycin are given in appropriate dosage.

The surgical approach is through the thorax. That portion of the esophagus containing the growth is freed, and the abdominal cavity is opened by incising the diaphragm at the esophageal hiatus. The esophagus and growth are resected. The stomach is freed sufficiently from its attachments to enable it to be brought up without tension into the thorax, and an anastomosis is made between it and the proximal end of the severed esophagus (Fig. 79).

Our results in this procedure are sufficiently encouraging to warrant further effort. One patient is living and well three years after resection, and several others are living from a period of a few months to two years after operation. We feel that the procedure offers a measure of hope, at least, in a previously hopeless condition.

MEDICAL ASPECTS OF INTESTINAL OBSTRUCTION

GEORGE CRILE, JR., M.D., F.A.C.S.

IF intestinal obstruction occurs in the first week following an abdominal operation or in the course of an acute intra-abdominal inflammatory disease such as appendicitis, it is likely to be the result of ileus and plastic exudate. Decompression with the Miller-Abbott tube effectively relieves such obstructions. If, on the other hand, intestinal obstruction occurs without a history of coexisting peritonitis, it is most likely to be the result of a mechanical obstruction which cannot be corrected by decompression and which sooner or later will demand surgical intervention. The most important task of the physician is to determine the type of obstruction present and not to try to treat by medical means cases in which the obstruction is mechanical and threatens the viability of the bowel.

When the diagnosis of mechanical obstruction, such as a violin-string type of band, a volvulus, an intussusception or a hernia, can be made in the first few hours, before distention has occurred and while the patient is still well hydrated and has not lost large amounts of chlorides, immediate operation is indicated. Valuable time may be lost if correction of the obstruction is deferred in order to attempt decompression of the bowel. But if distention and dehydration are present and if chlorides have been lost by vomiting, it is preferable to prepare the patient for operation by decompression of the gastro-intestinal tract and by administration of fluids and chlorides.

The two most important considerations in passing a Miller-Abbott or Harris tube are the foresightedness of the attending physician and the intelligence, industry and perseverance of the house officer or nurse to whom the technical details are delegated.

Perhaps more important than the details of passing the tube is the time at which it is passed. If delayed until the patient is distended, too ill to cooperate, and until the ileus is so marked that the bowel has lost its tone, the procedure may be exceedingly difficult. Under these circumstances it is best to pass the tube under fluoroscopic visualization, using a balloon containing 3 or 4 cc. of mercury or a Harris single lumen mercury-weighted tube. The tube may then be passed promptly under visual direction. Once it is through the duodenum difficulties rarely are encountered.

If the tube is passed before operation in those cases in which the development of peritonitis or intestinal obstruction is considered likely, the entire procedure is facilitated. Similarly, it is much easier to in-

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troduce the intestinal tube immediately after an operation such as appendectomy for a ruptured appendix than it is to try to pass it two days later when peritonitis is well established. If intestinal intubation is instituted successfully, the major problem of peritonitis is under control.

FLUID THERAPY

Coller's[1] classic studies of fluid balance have been widely accepted, and few will find fault with his thesis that sufficient water should be provided each day to allow for (1) loss of 1500 cc. of fluid from the skin and lungs, (2) replacement of fluids lost by gastric suction, vomiting, diarrhea, biliary drainage and the like, and (3) output of 1500 cc. of urine.

The amount of fluid required in the average postoperative case according to these standards is 3000 cc., but when the loss of fluid from the gastrointestinal tract is large, the replacement must be maintained at a proportionate level, even if this requires the administration of enormous amounts of fluid. If a patient is losing 4000 cc. of fluid a day by gastric suction there need be no hesitancy in replacing this fluid and/or providing a positive balance by giving 7000 cc. or more of fluid a day. When fluid is needed, the administration of water can do no harm.

In some quarters there is undue hesitancy in giving fluid for fear of "waterlogging" the patient. I believe it is very difficult to give too much fluid orally in the form of water. The ill results generally attributed to ingestion of water are usually the result of the excessive amounts of salt which are given with it. If administered intravenously, provided that the water is given slowly and with 5 per cent glucose, the risk of overdosage is equally small except possibly in patients with severe renal or myocardial disease.

If a large cannula is inserted into the jugular vein of a dog and saline solution is run in as fast as possible until the dog dies, immediate autopsy shows that the dog dies not of cardiac failure or of pulmonary edema but as the result of an enormous distention of the entire gastrointestinal tract with fluid. The fluid pours from the blood vessels into the lumen of the gastrointestinal tract and distends it to such a degree that eventually the mechanics of respiration are impaired, and the dog can no longer breathe. Although the lungs are damp and there is some free fluid in the peritoneal cavity, there is no frothy sputum indicative of true pulmonary edema.

With such a safety valve as this it is obvious that we need not hesitate to give fluid in as large quantities and as rapidly as needed, provided, of course, that it is truly needed. Possibly if the myocardium were abnormal and if fluid and salt were given rapidly over and above the needs of the patient, acute myocardial failure might be induced. Also, if an excess of fluid and salt were given to a patient with low serum proteins, edema might ensue. But when a patient

is dehydrated or in shock, fluid is needed and should be given until the desired physiologic response is obtained.

Too often in our desire to provide the patient with an adequate fluid intake we forget that the safest and best way to give fluid is by mouth. The salivary glands, the liver, the pancreas and the mucosa of the gastrointestinal tract secrete several pints of fluid daily, even when no food is taken. After the obstruction has been relieved it is not necessary to deny the patient the privilege of taking clear fluids by mouth. When 1000 cc. of glucose solution is given intravenously in less than an hour much of it is secreted into the gastrointestinal tract, just as in the case of the dog. The tendency of well-hydrated patients to complain of abdominal distention during the administration of glucose gives evidence that this is the case. Why, then, refuse to let the patient drink? And why give 1000 cc. of 5 per cent glucose solution containing only 200 calories to a patient who could easily take as many calories in a glass or two of milk? Intravenous therapy does not replace good nursing and dietary care after the obstruction is relieved.

Intravenous therapy, moreover, entails a small but definite hazard. Reactions occur occasionally following the intravenous administration of glucose regardless of the type of solution used. Although these reactions are rarely severe, I believe that a chill followed by a temperature of 103° or 104° F. has a detrimental influence on convalescence, and fatalities have been reported following the intravenous administration of glucose. I have observed a fatal case of gas gangrene following a hypodermoclysis and on another occasion an elevation of temperature to 108° F. following the intravenous administration of a solution of 5 per cent glucose in saline.

In some institutions the majority of patients subjected to operations receive glucose solution intravenously almost as a routine. During or following extensive operations this procedure is certainly indicated, but to give glucose to every patient after a pelvic laparotomy or an appendectomy when the patient should be able and willing to eat and drink is certainly introducing an additional hazard not warranted by the benefits obtained.

Similarly, the vogue for blood plasma and its ready availability has led to its use far beyond its indications. The literature has been so filled with references to the treatment of shock with plasma that many have forgotten that nine-tenths of the cases of shock were treated just as effectively with glucose and saline solutions before plasma was introduced. This does not refer to patients with lowered serum proteins resulting from extreme exsanguination from prolonged bleeding nor to the treatment of severely burned patients. It is in the simple case when, associated with spinal anesthesia or with acute hemorrhage, the blood pressure falls a few points that the pressure can be promptly and effectively restored to normal by giving glucose. The glucose is not only much cheaper, but is also much safer than blood-

bank plasma, following the use of which severe reactions are not uncommon.

Blood transfusion is a serious procedure and should not be undertaken without definite indications. There is always danger of inducing homologous serum hepatitis. A severe transfusion reaction may cause more damage than ten transfusions could repair. Fatal reactions following transfusion still occasionally occur. When a patient is well over a serious crisis and is convalescing normally, his hemoglobin will rise rapidly to normal levels. It is not at this time, even though his hemoglobin be 50 or 60 per cent, that transfusion is indicated. The time that blood is needed is *before* the crisis or *during* the crisis and *not* following it. This applies to hemorrhage as well as to infection, for it is rare that a single acute hemorrhage is of such severity that the patient is left anemic for longer than a month or two, provided his recuperative powers are normal.

The chloride balance of the patient is just as important as the fluid and protein balance.

When the chlorides of the blood are diminished the situation is comparable to that of a salt-water fish attempting to survive in fresh water. The cells adapted to a relatively high concentration of chlorides are not capable of functioning or even of surviving when their chloride contents are diminished below the critical level. The train of events that occurs in severe chloride loss can be summarized as follows:

1. Decrease in plasma and interstitial fluid volume in the attempt to maintain a normal plasma chloride level.
2. Decrease in plasma and interstitial fluid chloride concentration.
3. Disturbance of cell metabolism due to hypochloremia.
4. Resultant breakdown of cell protoplasm with increase in circulating nitrogenous wastes.
5. Failure of renal function, progressing to azotemia.
6. Added (toxic) disturbances of tissue metabolism associated with uremia.
7. Serious damage to liver and kidney cells.
8. Death in coma.

In intestinal obstruction, pyloric obstruction, peritonitis and acute small intestinal fistulas, large quantities of chlorides may be lost rapidly. Even if the serum protein level is maintained and the total fluid intake is adequate, serious and sometimes irreversible damage may take place if the lost chlorides are not replaced. This danger is a common one, and in such cases Coller's law, that chlorides should be replaced by the administration of 0.5 gm. of sodium chloride per kilogram of weight for every 100 mg. that the serum chlorides are below 560 mg. per 100 cc., is generally applicable. Moreover, as Collins[2] has pointed out, a tissue deficit of chloride may exist without reduction in the concentration of chlorides in the plasma and may

manifest itself solely by a reduction in the chloride excreted in the urine.

Coller[3] has revised his rule for replacement of chlorides and has emphasized the danger of basing treatment on the plasma chloride level to the exclusion of other factors. This is especially true in elderly patients, in patients with impairment of renal function, and in patients suffering from a suppression of urine. But these cases are the exception and not the rule, and we should not be led to over-react away from replacing lost chlorides for fear that each case may fall into this relatively rare category.

When renal function is normal or nearly so, the administration of sodium chloride serves to replace either a deficit in sodium or a deficit in chloride, for the ion which is needed to restore the body fluids to normal is retained by the kidney and the one which is not needed is rapidly excreted. When renal function is impaired this capacity for selective and rapid excretion is lost. The result is that both the administered ions pile up in the body. Such retention of chloride may add to the difficulties of the patient by causing a temporary chloride acidosis due to replacement of plasma bicarbonate, a weak acid, by chloride, a highly acidic ion.

Even if acidosis does not occur, the administration of sodium chloride in such amounts to a patient whose renal function is impaired is unphysiologic because the kidneys will be unable to excrete the excess salt. The retained salt must hold sufficient water to dilute it, and the resultant retention of water will produce edema.

Physiologic saline or Ringer's solution is not buffered, as is plasma, and as compared to plasma contains chloride ions in a ratio of 150 to 100. Thus in giving saline solution, even to a patient with normal renal function and with no acidosis, it is apparent that a mild tendency to acidosis is produced when the strongly acid chloride ions displace the weakly acid phosphates and lactates. Hence, "physiologic" saline is not in reality physiologic, and it is preferable to give it in two-thirds strength, made isotonic by added sodium lactate (approximately 1 liter of 0.9 per cent sodium chloride and 500 cc. of one-sixth molar lactate). This mixture approximates the composition of interstitial fluid and may be relied upon not to cause acidosis.

Coller's[3] premise (that by strict chemical standards the administration of saline solution is unphysiologic) is well founded. There are occasional cases with renal failure in which it is dangerous to give excessive amounts of salt. Nevertheless, these cases are the exception, and we need rarely hesitate to give saline solution in reasonable quantities. When the urinary output is over 1000 cc. daily, the problem of eliminating salt and maintaining a normal acid base equilibrium usually is solved by the kidneys. In short, the most important thing to know about a patient with a questionable fluid and electrolytic balance is his daily output of urine. If this is satisfactory the kidneys

usually may be relied upon to do the rest. If it is not satisfactory the greatest care must be exercised in artificially regulating the acid-base, fluid and electrolytic equilibrium. Since it is only in rare cases with impairment of renal function that a moderate excess of chloride intake is dangerous, since the vast majority of patients can excrete a moderate excess of chlorides without difficulty, and since chloride deficiencies of serious consequence are so common in patients who have been vomiting, it would be well to remember when in doubt to administer sufficient chloride to prevent the catabolic crisis of chloride deficiency. If an excess of sodium chloride is given, the kidneys will excrete it. If insufficient sodium chloride is given there is no reserve upon which the body can call to replace its losses. But when renal function is impaired caution must be used, and the electrolytic balance must be worked out carefully by trial and error and with due consideration to the dangers of giving too much salt.

When an excess of salt has been given and the patient is edematous as a result of secondary retention of water, the best way to eliminate the excess salt and hence the edema is to wash out the salt by giving large amounts of water. The intake of salt should be limited and the large amounts of water that are given will then result in the rapid elimination of the salt, and the edema will disappear.

The following table summarizes the treatment of fluid and electrolyte balance.

REPLACEMENT OF FLUID AND ELECTROLYTES*

1. Water loss	5 per cent glucose in water
2. Electrolyte loss	NaCl and trust the kidneys or Mixture of ⅔ NaCl and ⅓ sixth molar lactate
3. Ketosis	5 per cent glucose in NaCl if renal function is good; in sodium chloride and sodium lactate mixture if renal function is poor.
4. Acidosis	Sodium lactate if acidosis is severe enough to cause dyspnea (*3700 cc. ⅙ molar lactate required if CO_2 is 30 volumes per cent. Start with one half calculated dose and continue slowly).*

DIETARY MEASURES

Homer Smith[4] said, "The composition of the body is determined more by what the kidneys keep than by what the mouth ingests." Diseases such as the nephrotic stage of nephritis, when plasma protein disappears almost as rapidly as it is given and in which there is a lowered "set" of the serum proteins above which it is impossible to raise them, illustrate this observation.

* Corcoran, A. C.: Personal communication.

The complex subject of protein metabolism contains other illustrations of the impossibility of significantly altering the composition of the body by feeding. In starvation the negative nitrogen balance and the lowered serum proteins may be corrected by feeding protein or by giving amino acids intravenously, but in protracted debilitating illnesses or following severe trauma it is impossible to obtain a positive nitrogen balance and very difficult to effect any significant elevation of the serum proteins.

In the case of the lowered serum proteins found in nephrosis the lowered "set" of renal threshold for protein is probably adaptive and is designed to reduce osmotic pressure so that the filtration rate from damaged glomeruli can be maintained. No such adaptive purpose can be clearly visualized in the hypoproteinemia and negative nitrogen balance that accompanies trauma or debilitating disease, but interesting explanations of these phenomena have been made by Fuller Albright.

Albright[5] believes that in the presence of trauma or disease the "S," or sugar hormone of the adrenal cortex, is secreted in excessive amounts and that this, as in Cushing's syndrome, results in an inhibition of anabolic processes and hence in a negative nitrogen balance. He quotes Selye, who has described certain reactions of the body which occur as a result of any damaging agent, be it infection, burn, cold or trauma. Selye[6] emphasized that we must separate the specific reactions to these damaging agents from the nonspecific reaction which is common to all and which is termed the "alarm reaction." Selye defines the "alarm reaction" as the sum of all biologic phenomena elicited by sudden exposure to noxious stimuli to which the body is not adapted. The reactions which occur in response to trauma he considers to be fundamentally protective and adaptive.

During the alarm reaction one of the constant findings is hyperplasia of the adrenal cortex.

There is good evidence that it is the "S," or anti-anabolic hormone, rather than the "N," or tissue-building hormone, that is secreted at this time. The nitrogen balance during the alarm reaction is therefore negative no matter how much protein is given, and there is a measurable increase in the excretion and hence probably in the production of the "S" hormone at this time.

Albright believes that these reactions probably are purposeful and beneficial adjustments meant to curtail general tissue maintenance so as to provide building blocks for the repair of tissue at the site of injury. When the alarm reaction lasts too long, as in infections or debilitating diseases, this reaction becomes detrimental and leads to such generalized debility that it is quite possible that treatment with the "N"-like (nitrogen-retaining) hormone, such as testosterone propionate, might be indicated. In any case, little can be accomplished

by giving protein or amino acids while the stimulus of tissue damage persists and the patient remains in the "alarm reaction."

The anorexia of individuals during the acute stages of a disease now becomes understandable. Albright explains that if, under the influence of the "S" hormone, tissue maintenance stops and tissue breakdown continues at an ordinary rate, the body is flooded with tissue-building material and has no need of more from the outside. "Probably primitive man was unable to get food when injured and evolution has not kept pace with nursing care which now sees to it that calories are stuffed into the injured individual."[5] The food that is given under such circumstances probably has no more effect on the rate or security of healing than does the amount the mother eats influence the growth of the fetus or the amount that a patient with cancer eats influence the growth of the tumor. The repair of the injury, the demands of the fetus, and the growth of the cancer are provided for first without regard to the nutrition of the host. It would seem, therefore, that there is a practical limit to the role of diet and/or intravenous alimentation with amino acids as applied to the patient who is suffering from severe tissue damage.

In considering the failure of amino acids to restore nitrogen balance or to raise the level of serum proteins in seriously ill patients, it should be remembered that in starvation a different situation is encountered and that the intravenous administration of amino acid, as advocated by Elman,[7] is of definite value in maintaining nitrogen balance. Fifty grams (1000 cc. of 5 per cent amino acid in 5 per cent glucose solution) given intravenously each day along with 2000 cc. of 5 per cent glucose gives enough amino acids to maintain nitrogen equilibrium and 800 of the 1600 calories that are required. The remainder can be taken from the stores of body fat. In patients who are unable to eat, such therapy is of immense value, but when the patient can eat and assimilate there is no reason to believe that the intravenous administration of amino acids and glucose is of any value.

Another interesting sidelight on the problem of nutrition has been pointed out by Richter,[8] who showed that in both animals and man the effort to maintain a constant internal environment or homeostasis constitutes one of the most universal and powerful of all behavior urges or drives.

Richter removed the adrenal glands of rats, causing them to lose large quantities of sodium and die in from eight to fifteen days unless large quantities of sodium were given.

When salt was made available in containers separate from their regular diet, the adrenalectomized animals took sufficient salt to maintain life, 13 cc. as compared to 2 cc. for the controls. Moreover, when offered a variety of mineral solutions at the same time, the adrenalectomized animals selected the sodium salts and did not show appetite

for other chlorides. If the nerves to the tongue were severed to abolish taste the animals could not select and died.

From a study of appetite for cod liver oil in children, Richter suggested that the liking of the oil could be used as a means of detecting an appetite for and therefore a deficiency of vitamin A or D or some of the fatty acids.

If this is so and if animals and men can accurately select the food that they require, we should not disregard the patient's desires regarding diet and fluids. Whenever possible, food and fluid should be given by mouth, and it should be remembered that the patient himself is often in a better position to recognize his requirements and direct his activities and his diet than is the physician or the laboratory technician.

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ANEMIA IN DISEASES OF THE INTESTINAL TRACT

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EVERY patient with disease of the intestinal tract deserves a careful blood study.[1] Anemia is often a significant feature in such conditions. The reduction in red cells and hemoglobin may be due (1) to abnormal blood loss or excessive hemolysis of erythrocytes or (2) to decreased blood formation resulting from a toxic depression of the bone marrow by a wide variety of substances or from a lack of iron and the specific maturing factor, supplied by liver and liver substitutes, necessary for normal bone marrow activity.

An exact laboratory study of the blood often gives a clue to the cause of the anemia. If it is due to hemorrhage which is primarily iron loss or to some other iron deficiency, the cells first become deficient in hemoglobin, as indicated by a lowered color index. As the iron deficiency becomes more chronic and more severe the red cells become smaller, as indicated by a low volume index. Thus a mild iron deficiency causes a low color index while a severe one shows both a low volume and a low color index. With a loss of the specific erythrocyte factor normally found in the stomach and stored in the liver, the formation of stroma is impaired and the remaining cells are larger than normal (increased volume index). With excessive hemolysis or a simple depression of marrow the number of cells and the hemoglobin are decreased, but there is little variation from normal in the volume and hemoglobin content of the red cells (normal volume index 1.0, normal color index 1.0).

A significant loss of blood due to ulceration from infection or malignant disease in the small intestine necessarily produces a hypochromic and later a microcytic anemia. This is detected in a study of the blood and tests for blood in the stool. Extensive regional enteritis may produce such a picture. Ulcers in the duodenum, polyps in the small intestine, and bleeding from Meckel's diverticulum are other possible causes for abnormal blood loss. There is little toxic depression of bone marrow in such cases, so there is a pure iron deficiency anemia.

Disease of the small intestine may cause severe anemia without blood loss. *Pernicious anemia* was long considered to result from the toxic action on red cells of some toxic substance absorbed from the intestinal tract. This view is no longer held, since it has been proved that pernicious anemia is a deficiency disease due to defective formation of a specific erythrocyte-maturing factor (E.M.F.) in the stomach. This substance is normally present in the upper intestinal tract

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and is used by the bone marrow for building the stroma of red cells, or it is stored in the liver. If the specific maturing factor is lacking, the resulting anemia is always macrocytic unless the red cells are made smaller by a coincident iron deficiency.

ANEMIA DUE TO IMPAIRED ABSORPTION FROM THE SMALL INTESTINE

Macrocytic anemia may result from defective absorption of the specific factor in the small intestine. This seems to explain the macrocytic anemia seen so frequently in sprue. Both the anemia and the diarrhea of sprue are relieved by the use of a potent liver extract or of folic acid, which may be the active hematopoietic principle (E.M.F.).

In other conditions involving the small intestine, macrocytic anemia may also develop. With a benign obstruction of the lower small intestine a severe chronic macrocytic anemia indistinguishable from pernicious anemia may result. Regional ileitis with consequent scarring over a wide area may cause a similar anemia. This is especially likely to develop if some short-circuiting operation has been carried out. The fundamental defect so far as the anemia is concerned seems to be impaired absorption. The specific principle (E.M.F.) is formed, since free hydrochloric acid is present in the stomach. In pernicious anemia, where the specific principle is not formed, free hydrochloric acid is always absent.

The following two cases illustrate the development of macrocytic anemia due to impaired absorption of the specific principle from the small intestine.

Case I. Macrocytic Anemia Due to Obstruction of the Jejunum.—A housewife, aged 51, had had a hysterectomy, a laparotomy for a suspected ovarian tumor, and another operation for an acute intestinal obstruction. Nine years later she developed a resistant macrocytic anemia. Numbness and tingling of the hands and feet appeared, associated with generalized weakness. Physical examination revealed only impaired vibratory sense. Tests of liver function were normal. The red cell count was 2,910,000, hemoglobin 68 per cent (10.5 gm.), hematocrit reading 34 cc. per 100 cc. of blood (76 per cent of normal), volume index 1.3, color index 1.17, and the white cell count 5700. Repeated test meals demonstrated adequate free hydrochloric acid (free 47, total 48). Sternal puncture revealed a megaloblastic marrow. X-ray examination of the gastrointestinal tract disclosed an obstruction in the small bowel, with a lumen of about 0.5 cm., evidently due to adhesions.

Adequate parenteral liver therapy has maintained the blood count at normal levels. The neurologic lesion, though greatly benefited, has never completely cleared after treatment for several years.

Comment.—Impaired absorption of the erythrocyte-maturing factor (E.M.F.) produced a macrocytic anemia and neurologic changes, which have responded satisfactorily to liver extract therapy. The finding of free hydrochloric acid excluded pernicious anemia.

CASE II. **Macrocytic Anemia Due to Impaired Absorption.**—A man, aged 51, had had several extensive resections of the terminal ileum with anastomoses because of regional ileitis. Subsequently, abdominal distress had reappeared, associated with numbness and tingling of the hands. Vibratory sense remained intact. The general physical examination remained negative. X-ray examination showed a large area of obstruction secondary to the scarring of regional ileitis.

The red cell count was 3,830,000, hematocrit reading 42 cc. per 100 cc. (93 per cent of normal, 13.5 gm.), volume index 1.21, color index 1.13, hemoglobin 87 per cent, and white cell count 11,600. The mean cell diameter was 8.4 microns. An abundance of free hydrochloric acid was present (free 21, total 39).

Parenteral liver therapy was started with a subsidence of symptoms and return of the volume index to 0.96. On discontinuing liver extract injections a macrocytosis again developed. With folic acid alone numbness and tingling again appeared. The patient has remained symptom-free on continuous liver therapy.

Comment.—Lack of erythrocyte-maturing factor due to prolonged diarrhea and decreased absorption precipitated macrocytic anemia and early neurologic lesions, both of which have remained controlled with adequate liver therapy for several years.

ANEMIA IN CHRONIC ULCERATIVE COLITIS

Anemia is an almost constant accompaniment of chronic nonspecific ulcerative colitis, and the reduction in red cells and hemoglobin may be extreme. Relief of the anemia is a most important part of the treatment. A large part of the colon may be involved after the disease is well established. As the stools contain blood in varying amounts, the iron loss is considerable. With the chronic hemorrhage and consequent iron loss the hemoglobin is lowered out of proportion to the decrease in red cells. The anemia is hypochromic, and as the disease progresses the cells become small as well as deficient in hemoglobin, as shown by the low volume index.

The characteristic blood picture, then, in chronic nonspecific ulcerative colitis is a hypochromic anemia which may also be microcytic. The rapid passage of food materials through the intestinal tract in colitis interferes with absorption of all building materials, including the specific erythrocyte-maturing factor. A deficiency of this factor alone leads to a macrocytic anemia. If both iron and the specific principle are lacking the macrocytosis of iron deficiency is balanced by the macrocytosis of an erythrocyte-maturing factor-deficiency, so the cells are normal in size, even with a marked deficiency.

CASE III. **Hypochromic and Microcytic Anemia Due to Chronic Ulcerative Colitis.**—A woman, a pottery worker, had had severe diarrhea for eighteen months. She had passed some noticeable blood and had lost 87 pounds in weight. The only positive findings on the general physical examination were the evident anemia and impaired nutrition. The test meal showed a normal acidity. Roentgenograms of the colon and proctoscopic examination showed the typical findings of chronic ulcerative colitis.

The blood study revealed red blood cells 4,980,000, hematocrit reading 33 cc. per 100 cc. of blood (73 per cent), hemoglobin 8.9 gm. per 100 cc. (58 per cent), volume index 0.73, and color index 0.58. The white cells were normal.

The ulcerative colitis responded well to treatment, and as the condition improved the blood returned to normal. Ferrous sulfate was given in addition to treatment for the inflammatory process. The last blood count showed 4,670,000 red cells and 12.9 gm. (84 per cent) hemoglobin.

Comment.—This patient had a typical anemia of the iron deficiency type, as indicated by the low volume and color indices. The diarrhea, the infection, and the blood loss all played a part in the development of the anemia.

It is possible that a deficiency of vitamins, especially of B and C, may play a part in the anemia. The toxemia incident to the severe infection causing the colitis may also depress the normal development and delivery of red cells from the marrow. It is apparent that any type of anemia, hypochromic and microcytic, may be found in chronic ulcerative colitis, but by far the most common type is the hypochromic and microcytic anemia due to chronic blood loss and a consequent deficiency of iron.

TREATMENT OF ANEMIA DUE TO DISEASE OF THE SMALL INTESTINE

Before treating an anemia due to disease of the small intestine it is most important to determine the type present by complete laboratory study. If the anemia is hypochromic and microcytic, iron is indicated, if macrocytic, liver or liver substitutes are needed. If the anemia is due to toxic depression of marrow, transfusion is needed. Iron should be given in the ferrous form. I have long used a pill containing ferrous sulfate and sodium bicarbonate, which is much like the original mixture of Blaud. When absorption of iron is interfered with by an active inflammation or from some other reason, iron may be given intravenously. Iron cacodylate, 0.65 gm. (1 grain), is well tolerated. Iron may also be given in liquid form in the following prescription (Witts[2]):

Ferrous chloride	6 gm (90 grains)
Simple syrup	30 cc. (1 oz.)
Water	q.s. ad 120 cc. (4 oz.)

This is taken in teaspoonful doses containing 0.2 gm. (3 grains) of ferrous chloride after meals. The syrup is added to prevent oxidation of the ferrous iron. If absorption is adequate, anemia due to iron loss may be quickly compensated by administration of iron in adequate doses.

If the anemia is macrocytic, as illustrated in Cases I and II, liver or a liver substitute is indicated. Folic acid seems to be of benefit in sprue. Here there is seldom if ever any neurologic involvement, therefore the folic acid is a satisfactory substitute for liver. In pernicious anemia folic acid does not protect against a nerve lesion so should never be depended upon for treatment.

ANEMIA IN MALIGNANT DISEASE OF THE COLON

Cancer of the colon nearly always causes ulceration, which may result in sufficient mechanical loss of blood to produce anemia. Such an anemia is hypochromic and microcytic if the hemorrhage is prolonged or significant. A loss of blood, however, is not the principal cause for the anemia. It is unusual to have a marked anemia in cancer of the transverse or descending colon or rectum. On the other hand, cancer of the cecum and ascending colon almost always causes severe hypochromic and microcytic anemia all out of proportion to the blood loss. With an equal amount of blood in the stools and a carcinoma equally large, the lesion in the cecum will cause an extreme anemia, while the one in the rectum will cause only a minimal degree. In each instance the anemia is typical of an iron deficiency. It is evident that some factor in cancer of the cecum must prevent the utilization of iron by the bone marrow since the severe anemia may occur with little or no demonstrable loss of iron by hemorrhage. The hypochromic and microcytic anemia is thus due to impaired utilization of iron rather than to loss of supply to the marrow, where the iron is incorporated into the hemoglobin molecule and into the red cell.

The contents of the bowel in the cecum and ascending colon are liquid, hence a tumor in this area may become quite large before symptoms are produced. This allows a large surface area to develop for the oozing of blood and for toxic absorption. Alvarez, Judd, MacCarty and Zimmerman[3] came to the conclusion that this significant surface area is the most important factor in determining the frequency and severity of anemia in cancer of the cecum and ascending colon. There is evidently, however, some undetermined element operative in this location which is not dependent on the size of the tumor. Other diseases of the cecum, such as amebic colitis, tuberculous and regional enteritis, with changes in the mucosa affording large areas of active absorption, seldom give rise to a significant anemia.

While the anemia of cancer located in the cecum and ascending colon is typically hypochromic and microcytic it may occasionally be macrocytic. Butt and Watkins[4] have reported such a case; we have recently observed another.

The following case reports illustrate the anemia of cancer of the colon.

CASE IV. **Hypochromic and Microcytic Anemia Due to Carcinoma of the Cecum.**—A man, aged 67, had experienced progressive dyspnea and fatigue for the past two months. For one month he had noticed some generalized abdominal distress which had not been serious. His appetite was good, and there was no nausea, vomiting, constipation, or blood in the stools. The only significant finding in the physical examination was the evident anemia. No mass could be palpated. A roentgenogram of the colon showed a deformity in the cecum which was interpreted as being due to a malignancy.

The blood count on admission showed 3,520,000 red cells and 5.5 gm. (36 per cent) hemoglobin. A complete blood study after the first three transfusions showed

red blood cells 4,340,000, hematocrit reading 32 cc. per 100 cc. of blood (71 per cent of normal), hemoglobin 7.8 gm. per 100 cc. (51 per cent of normal), volume index 0.82, and color index 0.59. The white cell count was 7750 with a normal differential. The striking finding was the marked reduction in hemoglobin without a parallel decrease in red cells. The anemia was microcytic and hypochromic, as indicated by the low volume index (0.82) and low color index (0.59).

At operation a large tumor mass was found in the terminal portion of the cecum without metastasis to adjacent lymph glands or elsewhere. The pathologic sections showed a mucinous adenocarcinoma.

Numerous transfusions were given. Convalescence was complicated by localized abscess formation and prostatic obstruction. Recovery was complete. Two years later, signs of metastasis have not developed.

Comment.—The only significant symptoms complained of by the patient were due to the severe microcytic and hypochromic anemia. This finding should always suggest the possibility of cancer in the cecum or ascending colon. Although this anemia is of an iron deficiency type, it does not respond to iron therapy, indicating that it is due to lack of utilization and not to a deficient supply of iron. Transfusion helps temporarily, but the anemia is relieved only by removing the tumor, which, by some poorly understood mechanism, evidently prevents the utilizaton of iron.

CASE V. **Macrocytic Anemia Due to Cancer of the Cecum.**—A woman, aged 58, developed pallor, weakness, and shortness of breath over several months and seemed to feel improved after receiving liver extract. Physical examination, with the exception of pallor and some enlargement of the liver, was negative. Change in bowel habit had not occurred.

The red cell count was 2,900,000, hematocrit reading 29 cc. per 100 cc. of cells (64 per cent of normal), hemoglobin 47 per cent (7.3 gm.), volume index 1.10, and color index 0.91. The white cell count was 16,800. Sternal puncture showed erythroid hypoplasia. Gastroscopic examination revealed no abnormalities. A gastrointestinal x-ray examination revealed a deformed and contracted cecum. Stool specimens were repeatedly positive for occult blood.

The patient failed to respond to parenteral liver therapy, and a laparotomy revealed an inoperable carcinoma of the cecum. The macrocytosis continued to persist in spite of large doses of liver extract.

It is most probable that the macrocytosis in this case is due to impaired utilization of the specific maturing principle in the bone marrow.

SUMMARY

Anemia is a common accompaniment of diseases of the intestinal tract.

Proper treatment depends on a careful laboratory study.

The anemia of sprue and impaired absorption from the small intestine due to chronic obstruction or the end results of extensive regional enteritis is often macrocytic and responds to liver therapy.

If the anemia in disease of the small intestine is due to blood loss it is hypochromic and microcytic and should respond to adequate iron administration.

An anemia due to bone marrow depression by toxemia of infection or other factors is usually normocytic and responds only to removal of the cause and transfusion.

In true colitis, especially of the nonspecific type, the anemia is due to blood loss, depression of marrow function, and deficient absorption of materials needed for erythrocyte formation.

Anemia is uncommon in cancer of the transverse and descending colon and rectum.

A severe anemia of the hypochromic and microcytic type is almost constant in cancer of the ascending colon and cecum. While the anemia is of the iron deficiency type, it is not improved by administration of iron.

The anemia of cancer in this area is probably due to interference with the utilization of iron rather than to a loss of supply to the marrow. It disappears with removal of the tumor, although transfusions are a necessary preparation for operation.

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DIFFERENTIAL DIAGNOSIS OF INTRA-ABDOMINAL PAIN

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THE most important starting point in the differential diagnosis of abdominal pain is a painstaking, accurate, sequential history of the onset, character, location, duration and radiation of pain. This must be followed by a careful physical examination, study of the associated symptoms, clinical observations, and an intelligent choice of laboratory aids.

PERSISTENT OR CHRONIC ABDOMINAL PAIN

We must first try to establish whether the pain is present within or without the abdominal cavity. (1) Chest conditions such as pneumonia, pleurisy or coronary disease may simulate intra-abdominal conditions; (2) skeletal diseases, such as arthritis, myositis and neuralgias, may cause pain which may be confused with intra-abdominal disease; (3) conditions in organs behind the peritoneum in the kidneys, ureters or bladder may simulate intra-abdominal conditions. Finally, even disease within the scrotum, as epididymitis, or even a small testicular tumor may give rise to intra-abdominal metastasis with pain.

Chest Conditions.—Pain in the upper abdomen due to *pleurisy* or *pneumonia* is generally identified by the friction rub and associated symptoms of fever, increased respiration and other signs on physical examination of the chest. A roentgenogram will further confirm the diagnosis. *Coronary thrombosis*, with its occasional terrific pain in the epigastrium, may be confused with biliary colic. One factor in the differential diagnosis is that the administration of 16 mg. (¼ grain) of morphine will generally relieve the biliary colic, whereas 32 to 50 mg. (½ to ¾ grain) will frequently be necessary to relieve the pain of coronary thrombosis. Electrocardiogram and blood pressure studies will generally establish the differential diagnosis.

Skeletal Diseases.—The lower six thoracic and first two lumbar spinal nerves constitute the innervation of the abdominal wall, and symptoms of the involvement of these trunks may simulate those of intra-abdominal lesions. Failure to recognize this accounts for many failures in diagnosis when pain is the chief symptom. Carnett[1] forcibly demonstrated that *neuralgia* is caused by some form of abnormality resulting in inflammation or pressure on the spinal nerve root. The cause of symptoms produced by *scoliosis* and *postural defects* in girls and young women is often diagnosed as appendicitis and salpingo-oophoritis, and operations are performed with the result that pain is

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A positive malarial smear, however, is not a contraindication to exploratory operation. *Exanthema, typhoid, diabetes, lead colic* and *allergies* may simulate intra-abdominal disease if there is associated pain.

Cyclic vomiting, occurring particularly in children, if severe enough may result in the development of abdominal pain similar to that of diabetes with acidosis, tumors of the fourth ventricle, migraine,[6] and tabes dorsalis and may present a picture resembling acute surgical disease of the abdomen. Continuous vomiting will lead to ketonemia. Age is an important decisive factor in differentiating this condition from acute appendicitis. Appendicitis in children under 10 years of age is uncommon, and other causes for the pain must be determined. Furthermore, in any questionable case there will be no harm in delaying operation for a few hours, if necessary to confirm the diagnosis. In the meantime solution of glucose and saline administered intravenously will be helpful in the differential diagnosis. If there is no intra-abdominal disease the abdominal pain will soon disappear and the condition of the patient will improve considerably. If the pain persists or the tenderness becomes localized, it is quite likely that there is some diseased condition within the abdomen. If an operation becomes necessary the patient will have benefited from this management and will be a better operative risk. Also, in appendicitis the pain appears first and is followed by vomiting, whereas in the constitutional diseases pain follows the repeated vomiting.

In cases of *ulcerative colitis with ileostomy,* severe abdominal cramps may resemble symptoms of an intestinal obstruction and yet low blood chlorides may be the cause. Obviously, in a case of this kind where the cause is not recognized, laparotomy may lead to a fatality.

Extra-abdominal Causes.—If constitutional causes are ruled out, attention is next directed to the elimination of extra-abdominal causes. The heart, lungs, kidneys and intercostal neuralgias can be ruled out rather quickly by careful history and examination. If the cause is then narrowed down to an intra-abdominal cause it should fall within the following classifications: (1) colic, (2) hemorrhage, (3) obstruction and torsion, or (4) perforation or inflammation.

Colic.—In cases of colic, whether biliary, renal or tubal, the symptoms are striking, but diagnostic signs are surprisingly few. The patient will frequently volunteer the information that bending over with pressure on the abdomen makes him feel better. This is not true of other acute conditions where pressure increases the discomfort. In *biliary colic* the pain is generally in the epigastrium or right hypochondrium and is generally referred to the right scapular region. In patients who have had previous attacks it is frequently possible to elicit a history of residual soreness under the right rib for a day or two. In *renal colic* the pain is generally found in the flank and radiates down to the pubis and scrotum and is associated with urinary fre-

quency. In *tubal colic* resulting from extrauterine pregnancy, pain is felt in the lower part of the abdomen, with characteristic relief from pressure on bending over. Here the history and examination are highly suggestive of the diagnosis.

Hemorrhage.—When hemorrhage is present the pain is generally felt over the organ involved and is due to irritation of the peritoneum in that area. Hemorrhage from the liver and spleen results generally from injuries, though occasionally it may result from tumors of the liver. In ruptured tubal pregnancy or tubal abortion the pain is in the lower part of the abdomen. History, examination and blood studies will generally establish the differentiation.

Obstruction and Torsion.—In intestinal obstruction the pain is severe and colicky in nature and occurs in waves. It starts as mild distress, increases in severity, and gradually fades away. Usually the pain is rhythmic and the patient senses the onset. It is frequently described as similar to a "green apple bellyache." The pain is generally associated with nausea, vomiting and distention. Pressure over the abdomen increases the pain, and frequently the patient can point to the area of maximum tenderness, which will correspond to the area of obstruction.

In the small intestine the pain will usually be located above the umbilicus, whereas in the large intestine it will be general or below the umbilicus. If the obstruction is high in the small intestine vomiting is likely to occur early, owing to the large accumulation of gastric and biliary contents. If obstruction is low, vomiting occurs later.

Development of rigidity and tenderness, rapidly increasing pulse and elevation of temperature indicate interference of blood supply or strangulation. Mesenteric vascular occlusion is usually associated with profound shock and evidence of intraperitoneal fluid. However, varying degrees even of this condition must be recognized.

CASE I.—A white man, aged 60, was admitted to the hospital with the history that for the past two or three months he had noted occasional dull pain in the lower abdomen and in the right lower quadrant. One month prior to admission he had been hospitalized elsewhere because of severe periumbilical pain. At that time complete x-ray studies suggested only a poorly functioning gallbladder, and after ten days he was discharged. During the interval he remained well and was active except for anorexia and a single bout of diarrhea ten days prior to admission here. On the day of admission he developed severe pain in the right lower quadrant and vomited six times. He had a normal bowel movement that morning.

On examination the patient was in distress and perspiring profusely. His pulse was 110, temperature 101.3° F. The abdomen was thick-walled and distended, with marked hyperresonance in the left hypochondrium. Dullness was present over the flanks, and a tender, poorly defined mass was palpable in the right lower quadrant. Peristaltic sounds were diminished and faint. The white blood count was 9300 with 87 per cent neutrophils. Except for a blood urea of 48 mg. per 100 cc., the blood chemistry and urinalysis were within normal limits.

The provisional diagnosis was partial intestinal obstruction with an inflammatory mass in the vicinity of the cecum. A Miller-Abbott tube was passed into the small

bowel and constant suction started, with relief of distention but persistence of fever, mass, pain and ileus.

Two days after admission the abdomen was opened and a mesenteric thrombosis of recent origin involving 18 inches of the terminal ileum was found. The devitalized segment of bowel was removed and a side-to-side entero-enterostomy established. Further exploration of the small bowel disclosed a completely gangrenous segment 3 inches long either in the distal jejunum or proximal ileum, with an old localized mesenteric thrombosis. Because of the condition of the patient this segment was exteriorized through the wound and the wound closed with interrupted figure-of-8 steel sutures.

After operation the patient was given continuous intravenous heparin drip, the dosage being controlled by coagulation time determination every four hours. Dicumarol, 300 mg., was given simultaneously and followed by daily dosage of 100 mg. Heparin was discontinued on the third postoperative day when a satisfactory prolongation of the prothrombin time was obtained with the dicumarol.

With some difficulty because of the profuse discharge of intestinal fluids through the exteriorized bowel, the water and electrolyte balance was maintained by intravenous fluids and clysis.

On the twenty-sixth postoperative day a spur clamp was applied to the adjacent walls, and by the thirty-first day the continuity of the bowel had been established, so oral feedings were resumed and normal bowel movements occurred. However, leakage, with maceration of skin, persisted, so on the thirty-sixth day the open edges of the small bowel lumen were closed with interrupted black silk without attempting to restore the bowel to the abdominal cavity. At present leakage still persists but is diminishing, and skin maceration is subsiding. The patient is having daily stools, is in a good state of nutrition, and is ready for definitive anastomosis of the bowel and closure of the enterostomy.

Perforation.—Perforation of a viscus generally exhibits the clinical picture of an acute abdominal castastrophe. The pain varies according to the extent of peritoneal soiling. Early in the process the picture varies from considerable to profound shock. Twelve to eighteen hours later the patient states that he is feeling much better, and if he is not seen until this stage, procrastination must be guarded against.

Here a meticulous history of previous gastric, colonic, or menstrual difficulties, together with the nature of the present onset, is most valuable, and diagnostic procedures must be undertaken without delay. Unless prompt action is taken the third stage of spreading peritonitis will arrive all too soon.

Inflammation.—The areas that are the usual site of inflammatory processes are the pancreas, gallbladder, Meckel's diverticulum, appendix and colonic diverticula. Unless these conditions are fulminating, the pain is generally referred to as a bellyache. Early in the process the pain is rather vague but later it becomes localized. This is typical in *appendicitis*, where the pain occurs in the epigastrium or becomes generalized over the abdomen. Many cases of appendicitis are seen in the phase of epigastric distress and frequently are called gastrointestinal complaints. All too often the patient is given a cathartic. Such patients should be observed again in twelve hours to determine whether localization has occurred. *Chronic cholecystitis* and *chronic pancreatitis* produce vague upper abdominal complaints which, of

course, may have an acute exacerbation at any time. The picture of *acute hemorrhagic pancreatitis* is that of excruciating epigastric pain with rigidity of the abdomen and considerable degree of shock. However, there are gradations of this form of pancreatitis, particularly the type associated with disease of the gallbladder. In the past year we have encountered three cases of *acute cholecystitis* where there was tenderness over the entire abdomen which persisted for several days and subsided as the inflammation of the gallbladder abated. At operation fat necrosis was demonstrated in the three cases and in two there was hemorrhagic fluid in the lesser peritoneal cavity. Blood amylase studies during the acute phase give definite information. From the standpoint of differential diagnosis it is essential to stress the value of a survey film whenever feasible in any acute process within the abdomen.

Diverticulitis may be acute or chronic. The latter ordinarily is described as a soreness in the left lower quadrant. However, the soreness may be present throughout the lower part of the abdomen, because the sigmoid loop may often be in the midline or on the right side. Frequently in perforation of a diverticulum the diagnosis is that of acute appendicitis.

THE X-RAY IN THE DIFFERENTIAL DIAGNOSIS

Considerable aid may be obtained from survey films or so-called flat plates of the abdomen. Such a film must outline the diaphragm and also extend into the pelvis. In large patients two plates may be required. If the patient is not too ill, it is advisable to take a film in the upright position.

Free air beneath the right diaphragm is pathognomonic of rupture of a viscus. Free intraperitoneal air may arise from rupture of a peptic ulcer, but much more often the cause of free intraperitoneal air is rupture of an appendix or diverticulum. In such cases the previous history will generally aid in making the differential diagnosis. The amount of air pocketed will depend as a rule on the length of time since onset. A flat plate of the abdomen is also most useful in making or corroborating the diagnosis of obstruction in both large and small intestine. In obstruction of the small intestine there is the characteristic stepladder appearance of the dilated loops of small bowel. If the obstruction is high the degree of intestinal dilatation will be greater. In adults it is unusual to find gas in the small intestine, so that its presence, particularly in a patient with abdominal pain, must be looked upon with suspicion. Determination of a fluid level will further substantiate the diagnosis.

In sigmoidal obstruction, either acute from a long-standing diverticulosis with some inflammation, or chronic from the presence of carcinoma, gas may back up into the cecum resulting in overdistention which may even result in perforation.

CASE II.—A moderately obese white man, aged 62, was admitted to the hospital with the history that four days prior to admission he had experienced cramps across the lower abdomen which were persistent and which gradually increased in severity. Obstipation was present and was not relieved by successive enemas, although some gas was expelled. On the second day of the illness distention appeared and was accompanied by repeated emesis. The attending physician instituted constant gastric suction, with partial relief of the distention and the abdominal cramps. Examination with a barium enema at that time revealed an obstructing lesion of the rectosigmoid, with enormous distention of the proximal large bowel and cecum.

The only contributory facts in the past history were infrequent cramping pains in the lower abdomen during the preceding four or five months. No change in the bowel habit had been noted, and no blood, pus or mucus had been noted in the stool. There was no weight loss.

Examination revealed the abdomen to be moderately distended. There were no palpable masses or areas of tenderness. Occasional peristaltic rushes were audible. Digital and proctoscopic examination failed to disclose any pathologic condition of the rectum. The temperature, pulse and respiration were normal. Laboratory studies were within normal limits except for an elevation of the blood urea to 60 mg. per 100 cc.

On the basis of a provisional diagnosis of obstruction due to carcinoma of the rectosigmoid, preoperative preparation was instituted, but some distention persisted.

On the third day after admission a firm tender area was noted in the right lower quadrant and the possibility of an early rupture of the cecum was considered, although the temperature and white blood count had not become elevated.

Because of the development of this tenderness an immediate cecostomy was performed and a perforated cecum with large surrounding abscess was found. The abscess was evacuated and cecostomy established.

The patient improved immediately following the cecostomy. The blood urea dropped to normal. On the twenty-fourth hospital day a Mikulicz resection of an obstructing carcinoma of the lower descending colon was performed. Convalescence has been uneventful, and closure of the colostomy in ten weeks was anticipated.

A flat plate of the abdomen will also be helpful in cases of subdiaphragmatic abscess, intussusception and volvulus of the sigmoid. Obliteration of the ileopsoas line and scoliosis of the lumbar spine away from the affected side may give a clue to the possibility of perinephritic abscess if the clinical history also is suggestive.

CONCLUSION

In reflection, the physician and surgeon must be greatly impressed with the number of abdominal operations that have been performed without the relief of pain. Patients will ignore many intra-abdominal conditions which may necessitate operation as long as they do not have pain, but they are more than willing to submit to operation of whatever nature for the relief of this distressing symptom. If they are not relieved of pain and no definite cause for its presence can be found, patients frequently become mental problems with resulting conditions far worse than before operation. I think also that experience will bear out the conclusion that many of these patients have been operated upon for a chronic pain of long standing—and this finally is a reflection on accurate diagnosis.

One can indeed sympathize with the older clinicians in their problems of the solution of so-called "right sideitis" before the advancement of x-ray in the diagnosis of ulcer, disease of the gallbladder and of the kidney. However, of what value are the aids to diagnosis if they are not used intelligently? If a chronic right-sided pain is called appendicitis or tubo-ovarian trouble without the use of many diagnostic procedures at our command, then glaring errors will continue to be made. For instance, in cases of renal disease it is estimated that in 25 per cent or 30 per cent the appendix had been removed previously without relief of pain. In the differential diagnosis, if the kidney is not considered, then roentgenograms are not made and mistakes will continue. Whether the pain be acute or chronic, the condition is subject to the same rules of diagnostic procedure. However, in an acute abdominal disease occasionally a specific diagnosis cannot be made and early operation is safer than waiting for an exact diagnosis.

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THE DIAGNOSIS AND TREATMENT OF IRRITABLE COLON

Physiologic, Local Irritative and Psychosomatic Factors

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The syndrome of irritable colon is defined as a hyperirritable, neuromuscular imbalance of the colon sufficiently severe to cause abdominal pain or distress. Many synonyms are used to describe it, for example, unstable colon, spastic colon, spastic irritable bowel, functional bowel, mucous colic and mucous colitis, but the term "irritable colon" has been the one most frequently used by clinicians particularly interested in disturbances of the digestive tract. More than twenty-five years ago B. W. Sippy emphasized the fact that the term "colitis" was incorrect when there was no evidence of inflammation in the colon, and he coined the phrase "irritable colon."

The irritable colon syndrome is the most common cause and the most neglected entity pertaining to chronic abdominal distress. The distress may be so severe that narcotics are given, and appendectomy or cholecystectomy is sometimes mistakenly performed without, of course, relieving the symptoms. Ralph C. Brown[1] states, "It is my conviction that failure to recognize functional bowel disorders constitutes the single greatest source of error in abdominal diagnosis. Reference need only be made to the much-abused diagnosis of chronic appendicitis. At least one out of four cases of markedly irritable colon observed at the Presbyterian Hospital in Chicago will have had an appendectomy at some prior time." Frank C. Val Dez[2] says, "Colonic dysfunction is the chief cause of abdominal pain or discomfort. For many years colitis was used to designate colonic irritation. Sippy very early recognized that this term was not a proper one and used the designation "irritable colon" to describe such a noninflammatory disturbance."

Of 1000 cases of "unstable colon" studied by Jordan,[3] 73 per cent had a history of daily or frequent use of laxatives, enemas, or colonic irrigations; 38 per cent had no history of symptoms of neurogenic origin. Jordan states, "A patient in this group can therefore be regarded as having unstable colon because of local irritation, which, from the history of use of laxatives and the relief of pain with the omission of all measures to produce abnormal contraction, may justly be ascribed to catharsis."

Bockus and Willard[4] found some type of functional colonic disorder in 462, or 46 per cent, of 1000 consecutive case records of office patients.

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In review of 1000 consecutive cases at Cleveland Clinic, Collins and Van Ordstrand[5] found that 302 operations had been performed on 204 of the patients prior to admission without relief of symptoms. Appendectomy had been performed in 163 cases, thirty-eight operations had been performed on the biliary tract and another thirty-eight operations on the pelvis, without any change of symptoms. The most important etiologic factor in 445 cases, or 44.5 per cent, was local irritation due to an excess of roughage in the diet or to the use of cathartics and/or large irritating enemas.

During the past twenty-five years I have been primarily interested in dysfunction of the gastrointestinal tract due to functional as well

Fig 80.—Roentgenogram showing very spastic left colon. Repeated stool and proctoscopic examinations revealed normal findings in this case. The patient had taken daily cathartics for twenty years.

as to organic causes. I believe that physiologic considerations have not been given adequate attention. It is easy for the physician to tell the patient he has "colitis" and prescribe another cathartic or a special form of "colonic irrigation" to save time, but this does not settle the patient's problem. The purpose of this communication is to emphasize physiologic, local irritative, and psychosomatic factors and to help the clinician who first sees the patient. Much suffering and many needless operations can be prevented if the clinician will take time to recognize the irritable colon syndrome and base his diagnosis and treatment on physiologic principles.

PHYSIOLOGY; LOCAL IRRITATION

The intelligent patient appreciates learning the normal physiology of the colon as applied to his particular problem. Although the colon is primarily an organ of storage, a certain amount of absorption also occurs, particularly in the right colon. This absorption includes fluids, minerals and certain vitamins. When the intestinal content enters the cecum it is in a fluid state, and by the time it reaches the rectum it is normally soft-formed. A cathartic irritates the colon, induces rapid transit of the stool through the colon, and results in liquid stools. When this has been a daily occurrence over years of time, the mechanism of the rectal reflex, "nature's call," may be disturbed. If the patient suddenly stops using cathartics and allows normal time for the passage of food through the digestive tract, when the residue reaches the rectum he may not be cognizant of this fact. It may remain in the rectum too long, and impaction may result from the absorption of too much fluid. To prevent impaction the rectum should be emptied each day. Normal persons usually have a habit time for toilet routine, allowing sufficient time and relaxation, and go to stool at a regular time each day, usually after breakfast. As an aid in reestablishing a normal rhythm, the temporary use of a bland bulk-producer, such as one of the karaya gum preparations, may be beneficial. Ivy and Isaacs[6] have carefully analyzed these preparations and have found that their use does not prove harmful. At the beginning of treatment it may be necessary to start the bowel movement by inserting a glycerine suppository or a piece of soap in the shape of a suppository at the habit time. Patients who have been taking enemas may prefer to use a small rectal injection of plain warm water. A 3-ounce soft rubber ear bulbful may be sufficient, but no more than a pint should be used at any one time. The process of reeducating the rectum to a habit time should not be an ordeal. The patient should be instructed not to strain and advised that if the previous stool was loose (from the use of a cathartic) no stool may be obtained for several days because of previous overemptying of the colon. Those who have used large irritating enemas may be benefited by using 3-ounce oil retention enemas at bedtime at the beginning of treatment. Olive oil, sweet oil or mineral oil may be used. We advise against the oral use of mineral oil or cathartics.

As long as the rectum is emptied each day there need be no fear of constipation. Nature will take care of the bowel above the level of the rectum. If the intelligent cooperative patient will carry out these simple procedures every day for two or three weeks, he need have no worry relative to bowel function during the remainder of a lifetime.

The presence of constipation or diarrhea does not indicate an irritable colon. Many persons have constipation and take irritating cathartics for years without experiencing abdominal distress; others have

diarrhea. Although the patient having an irritable colon commonly complains of these symptoms, neither may be present. By definition this hyperirritable neuromuscular imbalance must be the cause of the abdominal distress, regardless of bowel habit.

The diagnosis must be made by the process of exclusion. All the local, systemic and reflex organic causes of distressing colonic spasm or dysfunction must be excluded.

PSYCHOSOMATIC FACTORS

A hypersensitive nervous system in general reacts more severely than normal to all manner of stimuli, so that the symptoms referable to the colon may be only part of a general nervous state. In 20 per cent of the present series of cases etiology was purely psychosomatic in origin, while in 32 per cent the cause was attributable to a combination of local irritations and psychosomatic factors. In a comprehensive study of sixty cases of mucous colitis, White and Jones[7] demonstrated the role of emotional tension as a precipitating factor. They concluded that in both instances the syndrome appears to be a somatic response to a type of nervous tension, but a number of conditioning factors play a role in the production of the symptoms, such as direct irritants of the colon, including rough foods, cathartics, enemas and coincidental colonic infection. In patients having a marked psychosomatic state, services of a psychiatrist are invaluable.

Bockus and his associates[8] have emphasized that this condition is one of the disorders of civilization. It is common in the more emotional races, or among the so-called "sentimental stock." Fatigue, as well as nervous stress and strain, often is provocative of attacks in susceptible persons, and upper respiratory infections may cause an acute exacerbation of symptoms. Bargen[9] states, "Our present-day life, with its hustle and bustle, its tremendous competition in wage earning, and its every urge for speed, often interferes with proper care of intestinal function. There results, therefore, a 'nervous indigestion' in which the colon plays no small part. After a morning rush to the office there is often an all-day rush in a highly competitive business. A person does not have time to stop for evacuation of the bowel. There is improper intake of fluids, the noonday meal is eaten hurriedly and under the most adverse conditions. At night such a person probably eats his dinner hurriedly to prepare for the evening's activities. He retires late only to arise again improperly rested and to go through the same procedures as on the previous day."

SYMPTOMS

In our review of 1000 consecutive cases, in most instances a long history of recurring bouts of abdominal discomfort related to irregular bowel habits was the presenting complaint. The intensity of the dis-

tress varied, the most familiar example of severe intestinal colic being the well-known "green apple bellyache" of childhood. When the distress is severe the symptoms are similar to those of chronic ulcerative colitis, diverticulitis of the sigmoid colon, or may simulate either biliary or renal colic.

The frequency of misdiagnosis is illustrated by the number of cases in which physicians do not recognize the symptoms in members of their own families. I have seen physicians' wives who had become morphine addicts as a result of improper therapy. At least thirty-one patients in this series had been receiving hypodermic injections of various opiates instead of proper management of the condition actually present.

The average duration of the symptoms was eight years. Usually the distress varies from a shifting cramplike pain to a sense of fullness, often associated with gaseous dyspepsia, that is, abdominal distention, rumbling and gurgling, belching and excessive flatus. The patient often complains of "difficulty with the bowels," namely constipation or diarrhea. However, as mentioned previously, the bowel habit may be normal. The patient may have observed large amounts of mucus or mucous casts in the stools.

Location.—The distress may be localized in any part of the abdomen along the course of the colon, although it is most often found in the left lower quadrant. There is often a shifting distress across the lower region of the abdomen which may move across the upper part or shift from one quadrant to another. The symptoms may be localized in the right lower quadrant, simulating appendicitis or terminal ileitis, in the right upper quadrant, simulating cholecystitis, or in the epigastrium or left upper quadrant, simulating diseases of the stomach or duodenum. Also, because of colonic distention in the upper left quadrant, in many of our patients a diagnosis of profound cardiac neurosis or "irritable heart" had been made.

One hundred sixty-one of the 1000 patients experienced pain in the lower part of the back associated with bowel function at the time of the abdominal distress. In these instances there was no muscle spasm of the back muscles or limitation of back movement.

Time of Day.—The maximum distress occurs during the hours of greatest intestinal activity, such as in the early morning hours and immediately after eating (gastrocolic reflex). Many patients hesitate to eat for fear of precipitating pain, distress or marked bloating. They often say that as long as they do not eat they are all right.

When the distress is noted in the right or upper part of the abdomen the patient may not associate it with colonic function. When loose stools result from cathartics the pain is usually increased. Many patients cannot tolerate a cathartic. There may be many associated symptoms, such as the hyperacidity syndrome, nervousness, insomnia, weakness, dizziness and headaches. Obviously the clinician will have

difficulty in the proper interpretation of the symptoms presented by a patient who does not speak his language or who has a low intelligence quotient and is therefore a poor observer. In these instances he must rely only on objective examinations.

Duration of Symptoms.—In cases of neoplastic disease the symptoms are usually continuous over a relatively short period of time. Patients having chronic ulcerative colitis (nonspecific) or peptic ulcer usually present symptoms which have been present over a long period of time, but they invariably have had complete remissions over months if not years of time during this period. In our review symptoms have been noted at least some time during every week for an average period of eight years.

PHYSICAL EXAMINATION

The physical examination is important in excluding organic disease. The positive findings often include a tender, ropelike sigmoid colon, regardless of the location of symptoms, often associated with a distended, somewhat tender cecum. There may be a generalized abdominal hyperesthesia. When the pain is localized, parietal abdominal neuralgia due to postural strain or spinal abnormalities must be considered. Tenderness due to a spastic irritable colon usually is deep and is elicited only when pressure is exerted directly over the colon.

DIAGNOSIS

I agree with Tumen,[10] who states that greater medical skill is required to recognize the existence of irritable bowel conditions and to instruct the afflicted patient in ways of management than is needed to prescribe a laxative. The prerequisite for correct diagnosis of irritable colon is that the attending physician be aware of the actuality of such a disorder; the basis of successful treatment is education of the patient in rudimentary bowel physiology. More than half of the number of cases of mucous colitis are misdiagnosed; conversely, more than half the patients initially labeled as having chronic gallbladder disease are eventually identified as having unstable colonic function.

The differential diagnosis of irritable colon must be made by the process of exclusion. A clinician particularly interested in disturbances of the digestive tract must consider many causes for disturbances in colonic function. The special studies indicated will depend upon careful analysis of the individual problem. If the patient has symptoms pertaining to the urinary tract as well as to the digestive tract, adequate examination of the urinary tract should, of course, precede the administration of barium sulfate in the investigation of the digestive tract. There may be a stone or other lesion in the genitourinary tract which causes a toxic or reflex influence on the colon.

DIFFERENTIAL DIAGNOSIS

Among the organic conditions to be excluded are:

1. Disease of the anus, rectum, and colon: hemorrhoids, anal fissure, polyposis, parasitic disease, chronic ulcerative colitis; lymphogranuloma venereum.
2. Extracolonic disease which may cause a toxic or reflex influence on the colon.

(a) Intra-abdominal: biliary or pancreatic disease; peptic ulcer; chronic gastritis; stone in the urinary tract, renal colic, uremia; regional enteritis; tumors of the small intestine; pelvic inflammatory disease, endometriosis.

(b) Extra-abdominal: chronic infectious diseases; systemic diseases; lesions of the central nervous system; syphilis; pulmonary disease.

3. Deficiency states: sprue, pellagra, pernicious anemia; anorexia nervosa; self-restriction of foods by food faddists.
4. Endocrine disease: premenstrual and menstrual disturbances; menopausal syndrome (male and female); thyroid disturbances; Addison's disease; parathyroid disease.
5. Gastrointestinal allergy.

Of first importance in the process of excluding organic disease is the careful evaluation of a detailed history, physical examination, always including the digital examination of the rectum, proctosigmoidoscopic examination, and roentgen examination of the colon, using the barium enema under fluoroscopic control. However, the diagnostic importance of roentgen examination should not be overrated, as it is of little value when dealing with abnormality below the sigmoid colon, although it is of great value when dealing with lesions above this area.

When local organic causes for dysfunction of the colon and rectum have been excluded such procedures as cholecystography, roentgen examination of the upper digestive tract, including detailed interval x-ray examinations of the small intestine, may be indicated. In special instances gastroscopic as well as duodenal drainage examinations may be indicated. Other special studies may be necessary to exclude the possible presence of organic conditions previously mentioned.

Included in the diagnostic criteria is the fact that the distress is usually increased immediately after eating and taking cathartics, such as magnesium sulfate for warm stool examinations. During the proctosigmoidoscopic examination unusual spasm may be seen, and the abdominal distress may be accurately reproduced. Occasionally the mucosa appears congested; unusual spasm, excessive mucus and/or melanosis coli may be present. During the administration of the barium enema under fluoroscopic control the distress may be aggravated as the barium sulfate suspension enters the colon and be relieved with its expulsion. The left colon may be unusually spastic

and the right colon unusually atonic. There is no shortening of the longitudinal axis, as is the case in chronic ulcerative colitis. Cold milk will relieve abdominal distress due to peptic ulcer but may aggravate distress due to irritable colon. A hot drink, application of an electric pad to the abdomen, or a hot tub bath often relieves the symptoms due to irritable colon.

In the process of exclusion, usually the clinician only needs to exclude organic disease in the rectum and colon, particularly if the history is of repeated long duration, the causative factors are definite, and the symptoms are typical for irritable colon. Then, if the patient follows the prescribed management and does not obtain satisfactory results, the clinician must make further studies to convince himself, as well as the patient, that no organic disease is present.

GENERAL TREATMENT

The selection of proper treatment should be highly individualized according to the severity of the symptoms and to the type of disturbance pertaining to physiologic function. The clinician should be firm in his convictions and his advice to the patient. When the disturbance is mild and is due to fear of organic disease such as cancer or to a neurogenic factor which can easily be eliminated, reassurance alone following a thorough examination may result in a complete relief of symptoms.

The basic principles of treatment include reassurance, relaxation and reeducation, including reeducation of the rectum to a habit time. When dealing with a cooperative patient a good prognosis can be given if the chief causative factor is local irritation, such as an excess of roughage in the diet or the long-continued self-use of cathartics or irritating enemas.

Any cause for enforced bed rest, such as operation or severe injury, may be an important factor in acquiring the pernicious cathartic or enema habit. Many hospitals maintain a routine "cathartic list," that is, administration of a cathartic on the night of any day there is no bowel movement, which starts the process of constant overemptying of the bowel. Seventy-two, or 7.2 per cent, of the patients in our review stated that their symptoms started immediately after an operation, 3.7 per cent after childbirth, and 2.2 per cent after enforced bedrest due to serious accident or other causes.

SPECIFIC TREATMENT

To intelligent patients the nature of the illness will need to be explained. On the other hand, there are individuals who are too "colon conscious." In these individuals care should be taken not to center too much attention on colonic function. The disorder may be only part of a general nervous state, and the aim of treatment is to make the patient eventually "colon unconscious." The patient should follow

a well-planned program and otherwise "forget the colon." Many of these individuals have unusual nervous tension and irregular habits in general.

Rest.—While reestablishing normal habits emphasis must be placed on adequate rest. A good night's sleep is important even though hypnotics may need to be used at the start of treatment. A period of complete bed rest, midday rest periods, more time in bed during weekends, or a vacation may need to be arranged according to the severity of the condition. Antispasmodics and mild sedatives are commonly used one-half to one hour before meals at the start of treatment to attenuate the gastrocolic reflex and to afford complete relaxation. When a reflex hyperacidity syndrome is due to an irritable colon, antacids such as aluminum hydroxide gel with magnesium trisilicate should be given in liberal amounts one hour after meals and as needed for the relief of hyperacidity symptoms until bowel function returns to normal. The patient should have rest before and after eating, and if the distress is severe an electric pad should be applied to the abdomen.

Diet.—Patients having irritable colon who believe they are suffering from constipation commonly use high-residue diets, including much roughage, such as bran and raw apples. They may not realize that this practice is similar to using irritating cathartics or large enemas and often increases the tendency to constipation by increasing spasm in the colon. If the abdominal distress is severe we use a nonresidue diet at the beginning of treatment, gruels made thin with water (not milk) of rice, farina, barley or Cream of Wheat, taken as often as desired for two or three days. The diet and all factors must be highly individualized. If the abdominal distress is less severe a high protein, high carbohydrate, low residue diet is advised at the beginning of treatment. No vegetables or fruits are allowed until symptoms are relieved. Then cooked vegetables and fruits are added gradually, according to tolerance, and finally the raw forms, until eventually the patient is on a well-balanced diet. In most instances the patient can tolerate cooked vegetables and fruits and with continued relief of symptoms can add the raw forms within a period of two or three weeks.

Regular Habits.—In order that patients having an irritable colon may obtain satisfactory results from treatment they must reestablish regular habits of adequate rest and relaxation, regular hours for eating and toilet routine. Meal hours should be cheerful. Emotional upsets and acute upper respiratory infections should be avoided. These truisms need constant reemphasis while the clinician is carefully supervising the patient's management.

Many men with this disorder work in shifts, and it is difficult for them to reestablish normal rhythm. In these instances we write letters to employers and do everything possible to favor normal habits.

Hospital Management.—In moderately severe or severe cases of irritable colon hospitalization is advisable This permits the use of observation tests at the times of the abdominal distress The details of strict management can be supervised, and daily observations will determine the most effective treatment. Daily digital examinations of the rectum will reassure the patient. Daily stool examinations furnish evidence pertaining to any disorder of digestion Rest and change of environment are important While the patient is being relieved of symptoms he is taught how to manage his particular problem by daily consultations Basic principles of treatment have proved as significant in this most common cause of chronic abdominal distress as they have in other conditions, such as the scientific control of diabetes

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AMEBIASIS AND INDETERMINATE ULCERATIVE COLITIS

Combined Therapy as Applied to Veterans from Overseas

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DURING and since World War II an increased number of patients have been seen with the usual findings of indeterminate or chronic nonspecific ulcerative colitis who have made a dramatic initial response to antiamebic therapy, even though evidence of amebiasis has not been found on repeated examinations. Most of these patients are men who have returned from the Mediterranean or South Pacific areas of combat. Following antiamebic therapy, sulfonamides and other forms of treatment for indeterminate ulcerative colitis have been used.

It is possible that the initial infection may have been due to amebiasis but that other invading organisms had changed the clinical picture by the time examinations were made. Monaghan[1] states, "Great difficulty may be encountered in those rare cases of chronic amebic dysentery in which a diffuse ulcerative colitis develops as the result of secondary infection of the colonic mucous membrane. Seven of thirty patients recently reported by Reed and Rochex[2] had amebiasis preceding ulcerative colitis, and other case studies in the literature record the presence of this organism in the early stage of the disease, subsequently diagnosed as ulcerative colitis."

Many of these patients present a hopeless attitude because of their severe disability. It would be helpful if everyone dealing with these conditions would report any favorable factor pertaining to management. The following case is typical of many patients we have seen.

CASE REPORT

A man, aged 27, was admitted to Cleveland Clinic Hospital by ambulance on January 21, 1947. He had been in another hospital for two months. He had had an attack of bloody diarrhea for a period of three weeks while in the Solomon Islands in 1943, and while on Guadalcanal fifteen months prior to admission he had developed severe bloody diarrhea with as many as fifteen stools per twenty-four hour period, as well as chills and fever to 102° F., anorexia, nausea and vomiting. At the time of admission he was in a serious condition and had lost 25 pounds in weight. He had been having continuous bloody stools night and day, and there was evidence of severe dehydration. The initial temperature was 101° F., pulse 120, and the skin was dry and ichthyotic. There was slight enlargement of the liver and tenderness along the course of the colon. The patient stated, "I have been in several hospitals and I am worse. I am going to die." A physician's attitude of hopelessness to such a situation is not warranted.

Numerous examinations of warm stools revealed considerable blood, pus and mucus, but no parasites. A report from a veterans' hospital disclosed that one stool

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examination had been "questionably positive" for Endamoeba histolytica, but repeated stool examinations thereafter had given no evidence of its presence Amebic complement fixation tests had given negative results. Sigmoidoscopy had shown an "erythematous mucosa with frequent small bleeding ulcerations consistent with the diagnosis of chronic ulcerative colitis"

In our examination diagnostic procedures were repeated and no primary etiologic agent was found. Smears from rectal aspirations and scrapings, cultures of stools and extensive blood agglutination studies did not give evidence of amebiasis, bacillary dysentery or other causative agents. The proctosigmoidoscopic examination revealed the characteristic findings of indeterminate ulcerative colitis

X-ray examination of the colon, using the barium enema, revealed extensive ulcerative colitis involving the entire colon and rectum with suggestive pseudopolypoid changes (Fig 81).

Fig 81.—Roentgenogram showing ulcerative involvement of entire colon.

The initial blood count was 3,960,000 red cells, hemoglobin of 8.3 gm., or 53 per cent, and 8200 white cells. The sedimentation rate of red cells was increased from our normal of 0 45 mm. to 0.95 mm per minute. The blood calcium was reduced to 8 9 mg. and the blood chloride to 495 mg. per 100 cc., but the blood phosphorus and carbon dioxide combining power of the plasma were normal. The gastric Ewald test meal revealed a free acidity of 10, a total acidity of 16. The blood Wassermann and Kahn tests were negative and the urinalysis gave negative results.

We considered this patient to have severe fulminating ulcerative colitis involving the entire colon. However, in view of the history, even though we could find no evidence of amebiasis, initial treatment included antiamebic therapy as follows: the intramuscular injection of emetine hydrochloride, 0.065 gm. (1 grain), daily for four days and at the same time one 0.25 gm. carbarsone capsule given orally three times daily for four days; this was followed by the oral administration of three

diodoquin tablets three times daily until fifty tablets were used. The response was dramatic, and the patient stated that it was the first time he had felt normal since the onset of his illness.

He was then given treatment for indeterminate or chronic nonspecific ulcerative colitis with the purpose of eradicating secondary invading organisms. This included

Fig. 82.—*Upper,* Roentgenogram seven months after one shown in Figure 81. No abnormality was found. *Lower,* Spot roentgenogram of cecum and terminal ileum showing normal findings.

1 gm. of phthalylsulfathiazole (*sulfathalidine*) four times daily as well as supportive therapy including blood transfusions, the oral administration of amino acids, a multivitamin preparation containing liberal amounts of ascorbic acid, and the use of vitamin K intramuscularly. The dose of calcium carbonate was varied according to the consistency of the stools. Antispasmodics were prescribed as needed for symptomatic relief.

The patient was discharged on the eighteenth hospital day, at which time he was advised to take 1 gm. of sulfathalidine four times daily for two weeks, followed by its withdrawal one week, in regular courses until his next office visit. He was also advised to continue the oral use of the amino acid preparation and multivitamins. A low residue diet high in protein and carbohydrate was advised.

Six weeks later he had gained 24 pounds, had returned to work, and felt well. He was having only one stool daily and was following a well-balanced diet. We therefore advised increasing the rest intervals between the courses of sulfathalidine.

Three months later his progress had remained excellent despite the fact that he had not taken medication for two months.

Two months later he had gained 45 pounds, he felt well, and his bowel habits were normal. He had taken no medication during this time and had been working regularly. Examinations of warm stools at this time revealed entirely normal findings, *as did the proctosigmoidoscopic examination and roentgen examination (Fig. 82).*

In view of this experience, which is not unusual in veterans from overseas, we believe an initial trial of antiamebic therapy should be made even though no evidence of amebiasis is found. Following such treatment eradication of secondary infection should be instituted, together with other therapy for indeterminate ulcerative colitis.

DIAGNOSIS

A diagnosis of intestinal amebiasis is made when the Endamoeba histolytica is isolated in stool or proctoscopic examinations. The history may be the same in patients having either amebiasis or indeterminate ulcerative colitis, that is, recurrent or persistent attacks of bloody rectal discharges. Our routine "colonic survey" in these instances includes examinations of warm stools (examined on a warm microscopic stage as soon as passed), proctosigmoidoscopic and roentgen examinations of the colon.

Stool Examinations.—If the initial warm stool examinations do not show evidence of amebiasis but reveal the presence of pus and blood, detailed cultures of the stools and blood agglutinations for the possible presence of bacillary dysentery and other causative agents are carried out. If the patient is not having diarrhea on the morning of the initial examination, Epsom salts are given so that material from the cecum (where the Endamoeba histolytica colonizes) may be examined. Repeated studies are important.* In our experience, the examination of a single "cold" specimen brought in by the patient is rarely helpful.

Proctoscopic Examination.—In acute amebic colitis the proctoscopic examination may reveal typical amebic ulcers which are discrete, have a punched-out appearance, and between which there is an absence of inflammatory changes. They usually vary from 4 to

* The authors are purposely avoiding details of parasitology in this communication. The comprehensive publications of Craig and Faust[3] and Banks[4] are recommended. The services of a parasitologist are invaluable. However, we found that warm stool examinations were most important in identifying the vegetative forms of Endamoeba histolytica, without the use of staining technic, and these examinations can easily be made by the general practitioner.

15 mm. in diameter but may be as large as 2 or 3 cm. in diameter with irregular margins and overhanging ragged edges. The ulcers may be covered by mucus and blood. After a cotton swab is used the characteristic appearance is observed and they are usually several centimeters apart, with normal intervening mucosa. Even when the Endamoeba histolytica cannot be demonstrated in warm stools it may be found in aspirations (Fradkin technic[5]) or scrapings taken from the base of the ulcer. However, it must be emphasized that at the Cleveland Clinic we rarely observe these typical proctoscopic findings, probably because of our geographic location and failure to observe an acute epidemic. Most of our patients present chronic disorders. The presence of secondary infection may have altered the proctoscopic findings or normal findings may be demonstrated on examination.

The proctoscopic findings in indeterminate ulcerative colitis are totally different from those observed in amebic colitis. There are no discrete ulcers with intervening normal mucosa. The mucosa presents a diffuse inflammatory process, is friable, and bleeds wherever the proctoscope produces pressure or a swab is applied. The valves of Houston are edematous and may be attenuated. The findings vary according to the stage of the disease in which the examination is made. The valves of Houston may be absent, or pseudopolyps may be observed with marked contraction of the lumen. The disease under consideration corresponds to Bargen's type 1, thrombo-ulcerative colitis,[6] which starts in the rectum as a diffuse, inflammatory, destructive and hyperplastic process and extends in an upward direction in the colon. Our experience also coincides with the clinical types described by Monaghan.[1] We believe Paulson[7] in his important contributions to this subject was the first to use the phrase "indeterminate ulcerative colitis." In approximately 93 per cent of our cases the disease starts in the rectum and extends proximally in the colon. No cases of regional enteritis, "right-sided" colitis, or segmental forms in which surgical therapy is usually indicated are included in the present discussion.

Roentgen Examination.—In our experience the roentgen examination presents normal findings in almost all of the patients who harbor Endamoeba histolytica. This examination, therefore, is important because of its negative value. In rare instances where positive roentgen evidence of amebic colitis is present the findings are those of other chronic ulcerative diseases pertaining to the cecum and ascending colon. There is shortening of the ascending colon and alterations in the mucosal pattern characteristic of ulcerative disease.

Part of our colonic survey in a patient presenting bloody diarrhea includes an x-ray examination of the chest. In adult persons tuberculous enterocolitis is rarely seen unless there is an open tuberculous process in the [illegible] when the roentgen examination of the chest in [illegible] reveals normal findings we believe tuberculous in-

volvement of the intestine can be excluded. However, if doubt remains, particularly when the roentgen examination reveals deformity of the terminal ileum or right colon, we make repeated stains for tubercle bacilli during stool examinations to exclude a possible bovine type of tuberculous involvement.

In indeterminate ulcerative colitis the roentgen examination using the barium enema may reveal normal findings when the process is limited to the rectum and sigmoid colon. However, this examination is very important in determining the extent of involvement of the colon, even though the extent of involvement does not bear any relation to the severity of the disease. If there is extension above the sigmoid colon the findings are in direct contrast to those observed in patients presenting positive findings for amebic colitis. In indeterminate ulcerative colitis the roentgen findings are characteristic of inflammatory changes in the left colon as contrasted with similar findings in the right colon for amebic colitis.

ANALYSIS OF 100 CONSECUTIVE CASES OF AMEBIASIS SEEN AT THE CLEVELAND CLINIC

It is well known that persons who live in tropical or subtropical areas present a higher incidence of amebic colitis than do those living in the Cleveland area. Therefore, we were interested in reviewing the records of 100 consecutive cases seen at Cleveland Clinic since World War II, in which the Endamoeba histolytica was isolated either by warm stool examinations or from material obtained from proctoscopic examinations. Only eleven of the 100 cases presented acute dysenteric symptoms at the time of our original examinations. No patient in this group presented the typical amebic ulcers surrounded by normal mucosa which are characteristic of amebic colitis, and only three cases presented roentgen evidence of amebic colitis by barium enema examinations, that is, evidence of ulceration of the cecum with shortening of the longitudinal axis of the right colon where the Endamoeba histolytica colonizes. Four of the eleven patients who had acute dysenteric symptoms presented proctoscopic and roentgen evidence of indeterminate ulcerative colitis. In one case the disease was limited to the rectum and sigmoid colon; in the other three cases the rectum, entire colon, and terminal ileum were involved. All four patients made an excellent response to the combined therapy previously mentioned. One patient was followed for twenty-seven months and another for sixteen months.

All of the 100 patients had had abdominal distress, the severity of which usually varied according to the number of stools passed per day. The eleven patients having acute dysenteric symptoms had severe cramplike pain either in the right lower quadrant of the abdomen or shifting across the lower abdomen, worse [illegible] after eating, and temporarily relieved by [illegible]

fever as high as 101° F. had been present in these patients. Twenty-five, or one-fourth, of the 100 patients, had had recurrent or persistent attacks of diarrhea, usually eight to twelve stools per twenty-four-hour period. Only twenty of these patients had observed bloody rectal discharges or stools mixed with blood. No complication of amebic colitis, such as perforation or amebic hepatitis, was observed in this series.

Seventy-five of the 100 patients had normal bowel function and had only mild shifting abdominal distress, usually across the lower abdomen; occasionally the pain was limited to the right lower abdominal quadrant, and was temporarily relieved by the passage of flatus or a bowel movement. The symptoms were similar to those presented by patients having functional digestive disorders, such as irritable colon. The patients in this group were classified as having amebiasis in the latent form or carrier state. The isolation of Endamoeba histolytica proved important, because antiamebic therapy resulted in immediate relief of symptoms in all cases. There have been several recurrences which required a second course of therapy.

TREATMENT

In veterans from overseas who gave a history of recurrent attacks or persistence of bloody rectal discharges but in whom no evidence of amebiasis was found, a therapeutic antiamebic test was used. This included the intramuscular injection of emetine hydrochloride, 0.065 gm. (1 grain), daily for four days, and at the same time one 0.25 gm. carbarsone capsule was given orally three times daily for four days; this was followed by the oral administration of diodoquin tablets, 210 mg. (3½ grain), three tablets being given three times daily until a total of fifty tablets was used. This report is made because so many patients made a dramatic initial response. We concluded that the initial infection was probably due to amebiasis but that other invading organisms had changed the clinical picture by the time our examinations were made. Following antiamebic therapy, sulfonamides and other factors in treating indeterminate ulcerative colitis were used. We believe this program has been important in rehabilitating these individuals. Follow-up studies have been made in most instances and the relief of symptoms, as well as favorable progress as evidenced by stool, proctosigmoidoscopic and roentgen examinations, have been noteworthy.

In the 100 consecutive cases in which the vegetative forms of Endamoeba histolytica were isolated the treatment varied according to the severity of the disease. In the patients presenting acute dysenteric symptoms 0.065 gm. (1 grain) of emetine hydrochloride was given intramuscularly daily for six days, if well tolerated. The possible toxic effect on the myocardium, as well as the possible production of a peripheral neuritis, must always be kept in mind while administering emetine. At the same time one 0.25 gm. carbarsone capsule was given

orally twice daily until twenty capsules had been used. If there was any question of liver damage this preparation was withheld. We have observed no intolerance to the use of diodoquin, so this preparation was used in all cases. Following the use of carbarsone, or at the same time emetine hydrochloride was given intramuscularly, three diodoquin tablets, 210 mg. (3½ grain), to be given orally three times daily for ten days, were prescribed. In the patients who did not have acute dysenteric symptoms the same program was followed except that emetine hydrochloride was not used. In spite of the relief of symptoms all patients who give evidence of amebiasis are advised to return for progress examinations, or at least for warm stool examinations, one, three and six months after the initial therapy is started. As mentioned, there have been several recurrences in the series quoted which required additional courses of therapy.

During the past ten years sulfonamides have been used as an adjunct to the usual therapy for indeterminate or so-called nonspecific chronic ulcerative colitis at the Cleveland Clinic. Our experience with sulfanilamide retention enemas in 1937 and the use of other sulfonamides in subsequent years has been reported.[8, 9, 10, 11, 12] The use of routine examinations of stools, proctosigmoidoscopic and roentgen examination of the colon, using the barium enema, and in certain instances the use of air insufflation after the expulsion of the barium enema, has resulted in earlier diagnoses in patients presenting symptoms related to bowel function. When the disease is limited to the rectum and sigmoid colon or the left colon, succinylsulfathiazole (sulfasuxidine) given by retention enema has resulted in a better response than that following its oral administration. The fact that this drug is not absorbed from the digestive tract and has only a local effect is well known. At the present time we advise stirring four 0.5-gm. tablets in a glassful of warm water for use as a retention enema, two weeks on, one week off in regular courses, depending upon the proctoscopic examinations, regardless of the relief of symptoms. The rest intervals are gradually increased if the patient makes satisfactory progress. At the end of six months the patient may be taking these retention enemas only one week out of each month. When the ulcerative involvement has extended to all parts of the colon 1 gm. of sulfasuxidine is given orally four times daily, two weeks on, one week off, gradually increasing the rest intervals if satisfactory progress is made.

During a four-year experience the use of sulfasuxidine proved helpful in 115 cases, but in only fifty-five cases were we able to make progressive proctoscopic and roentgen examinations over a period of two years. All except three were treated as ambulatory patients. Ten made no improvement on medical management, and two of this group have had ileostomy. None have died. Four were improved, and forty-one of the fifty-five patients had had a complete remission during the two years. Of thirty-two early cases in which the disease was limited

to the rectum and/or the left colon and in which sulfasuxidine retention enemas proved significant, a complete remission occurred in twenty-eight cases.

In the fifty-five cases followed for two years, sulfasuxidine was used in intermittent courses not longer than a general average of eight and a half months. The average time since sulfasuxidine therapy has been discontinued is fourteen and a half months.

Emphasis should be placed on the fact that sulfonamides were used as an adjunct to the usual therapy. It is difficult to evaluate any single therapeutic measure in this disease because the plan of management has included well-known factors pertaining to rest, diet, vitamin and mineral deficiencies. The administration of blood transfusions and parenteral fluids in severely toxic cases is important. Mackie,[13] Willard, Pessel, Hundley and Bockus,[14] and many others have emphasized the need for a multiple approach in the treatment of indeterminate chronic ulcerative colitis. All authorities are agreed that the patient should rest in bed as long as fever or pronounced diarrhea is present. The clinician must emphasize good basic habits of living and pay particular attention to psychosomatic factors. If the diet has not been well balanced and has not included essential minerals and vitamins, supplemental minerals and vitamins should be administered. The parenteral use of crude liver extract, thiamine hydrochloride, nicotinic and cevitamic acids, as well as vitamin K, may be indicated. If the patient is vomiting all food taken by mouth, food may need to be withheld or a gavage diet given by a Levin tube. In most cases a diet high in protein and carbohydrate but low in fat, supplemented by the use of amino-acid preparations, has proved efficacious. At the start of treatment milk, vegetables and fruits have been withheld. After a few days cooked vegetables and cooked fruits are gradually added. After one or two weeks raw forms of fruits and vegetables and milk are gradually added if well tolerated. Food allergy must be given consideration in patients who present other allergic manifestations. When there is a calcium deficiency either calcium carbonate or calcium gluconate has proved helpful. Antispasmodics and mild sedation prove helpful at the start of treatment. No serum or vaccine has been used in the cases quoted.

Each patient presents an individual problem. The variable severity of the disease and the fact that it is characterized by spontaneous remissions of symptoms also makes the correct evaluation of a single factor in treatment impossible. Because of the severity of the disability and his desire to help every patient, the clinician seldom runs a control series to any single form of therapy. The patient may present evidence of irreparable damage at the time of the initial examination. No form of medical management can be expected to restore to normal the physiologic function of an intestine which has become contracted and deformed by disease of long standing. All that any drug can be

expected to accomplish is the control of symptoms due to active infection.

Penicillin, given by intramuscular route in large doses, has proved helpful during the acute stage of the disease in a few cases, but the hope that it would be of benefit in those cases in which the sulfonamides were not effective has not been fulfilled. Recently the addition of 100,000 units of penicillin to the sulfasuxidine or sulfathalidine retention enemas has proved beneficial in certain instances where the use of sulfonamides was ineffective. Preliminary results with streptomycin have not been encouraging.

Certain complications, such as stricture, polyposis, neoplasm and perirectal abscess, constitute definite indications for surgery. In pointing out other indications for surgery, Jones[10] has emphasized the fact that with each acute exacerbation of the disease it tends to extend to more proximal sections of the colon. When the disease is limited to the distal colon a colostomy in the midtransverse colon results in less disability to the patient than ileostomy. When the patient does not make satisfactory progress on medical management, possibly the earlier use of this procedure, in conjunction with the continued use of newer developments in medical management as they appear, would permit the gastrointestinal lumen to be reestablished later. In patients having a more extensive involvement, particularly those having a toxic process where ileostomy is performed, the ileostomy is usually permanent. Later, if the progress of the patient is not satisfactory, total colectomy, performed in stages, may be necessary.

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REGIONAL ENTERITIS: DIAGNOSIS AND TREATMENT

A Study of Fifty-five Cases Over a Nine Year Period

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The management of regional enteritis presents greater problems at the present time than does the diagnosis. Improved clinical interest and roentgenologic methods have increased the frequency and ease of diagnosis, as manifested by the relatively large number of cases being reported in the literature. Prolonged experience emphasizes the inadequacy of some of the previously accepted methods of treatment, and in some instances recurrences, serious complications, and extensive involvement of the intestine make present methods of management unsatisfactory. Failures in management are due primarily to the fact that the cause of regional enteritis is unknown.

A series of fifty-five cases of enteritis, terminal ileitis and enterocolitis is presented, emphasizing the main points in diagnosis and comparing the results of the various types of treatment employed in their management. These patients were seen at Cleveland Clinic between the years of 1934 and 1946. Fifty-three of the diagnoses were proved by operation. Forty patients have been followed from one to thirteen years, with the average duration of observation being 5.2 years. Of the remaining fifteen patients, seven died after operation. Six of these patients developed peritonitis and died within one to forty-three days. The other patient made a satisfactory immediate convalescence. However, after discharge from the hospital her progress was not satisfactory. She died five months later and at autopsy a large subdiaphragmatic abscess was found. No follow-up studies were made in the other eight cases.

There has been little added to the original description of the subjective and objective manifestations of this disease as reported by Crohn, Ginzburg and Oppenheimer in 1932.[1] Our observations relative to age, sex distribution and symptomatology correlate closely those of other authors.[1, 2, 3] In our group of fifty-five patients, the average age was 28.5 years. Twenty-nine patients were in the third decade. The sex distribution was fairly even, with thirty-one males and twenty-four females.

SYMPTOMS

The duration of symptoms varied from one month to fifteen years, twenty-nine patients having had symptoms for less than one year. The presenting complaints and their frequency are shown in Table 1.

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The majority of patients presented symptoms suggestive of ulcerative colitis, namely diarrhea with cramplike abdominal pain. Three patients had an acute surgical condition within the abdomen; one was suspected of having an acute diverticulitis with perforation, and two were thought to have acute appendicitis. At operation all were found to have regional enteritis. It is likely that the general practitioner sees more patients with symptoms and signs of acute appendicitis than we encounter in a referred type of practice. Five patients had symptoms suggesting partial intestinal obstruction. Roentgen examination revealed evidence of significant obstruction in the region of the terminal ileum in several others. One patient, a woman of 21, complained of swelling, redness and tenderness of the joints and fever of three weeks' duration. She also had a psoriatic type of skin eruption. During the course of her examination blood was found in the stools, and further studies revealed the presence of terminal ileitis, which was later proved by operation. Cases of unexplained fever without abdominal symptoms due to regional enteritis also have been described in the literature.

TABLE 1

PRESENTING COMPLAINTS AND THEIR FREQUENCY

	Cramplike Abdominal Pain	Significant Weight Loss	Diarrhea	Draining Abdominal Sinus
No. of Cases	40	33	27	14

Weight loss is often a striking feature of this disease. A 56 year old man had lost 80 pounds in a five month period of time and was suspected of having a carcinoma of the right colon because upon examination a mass was found in the right lower quadrant of the abdomen. At operation he was found to have an acute inflammatory process involving the terminal 12 inches of the ileum with an internal fistula leading to an abscess in the right colic gutter.

Perforation of the bowel with fistula or abscess formation was a common complication in this group of patients. Fourteen had external fistulas in the right lower quadrant of the abdomen draining pus and/or fecal material, two patients having several such openings. Eight had internal fistulas. Two of the latter had passed gas and fecal contents in the urine and upon examination were found to have vesicocolic fistulas. Four had tracts leading from the small bowel to abscesses in either the right psoas, right colic gutter, or pelvis. Another patient had a communication between the ileum and sigmoid while one had a fistulous tract between the ascending and transverse colon. There were no instances of free perforation with generalized peritonitis. This frequency of fistula formation probably gives a false

indication of the incidence because a large number of difficult surgical problems are referred to the Clinic.

PHYSICAL FINDINGS

The most common findings on physical examination are outlined in Table 2.

TABLE 2

PHYSICAL FINDINGS

	Palpable Mass	Fever	Abdominal Sinus Opening	Fistula-in-Ano
No. of cases	26	27	14	9

Forty-five patients had definite tenderness in the right lower quadrant, and in twenty-four an abdominal mass was palpated. Digital rectal examination disclosed a mass in the right side of the pelvis in two patients. Fever was usually of the low grade type of chronic infection; however, in those patients with abscess formation the fever was spiking in character and sometimes accompanied by chills. The external fistulous openings were usually small, but their connection with the bowel could be demonstrated by roentgen examination after the injection of lipiodol. Nine of the patients had fistulas-in-ano and seven more gave a history of a previous fistulectomy. Most of the patients were malnourished, and in nine emaciation was marked. Although signs of vitamin deficiency were not outstanding, one patient showed objective evidence of B complex deficiency and had subacute combined degeneration of the spinal cord.

ROENTGEN FINDINGS

The changes revealed by roentgen examination have been adequately described in the literature. Careful roentgen examination will usually demonstrate the flow of a thin stream of barium through the involved segment of the small intestine. This is the popular "string sign" first described by Kantor.[4] A typical case is demonstrated in Figure 83.

Roentgen study of the colon is essential in all patients suspected of having regional enteritis. In our experience the regurgitation of barium through the ileocecal valve during barium enema study has been a most helpful method of demonstrating this lesion, particularly when it is located in the terminal ileum. The colon examination also serves to demonstrate the presence of coexisting colitis with or without skip areas and may arouse suspicion as to the presence of this disease if the terminal ileum cannot be filled. If there is suspicion of regional enteritis, it is important to do small intestinal motility studies in addi-

tion to x-ray examination of the colon because in some instances this is the only means of demonstrating the lesion, particularly if it lies

Fig. 83.—Barium enema demonstrating retrograde filling of the terminal ileum with characteristic string sign due to terminal ileitis.

84.—Evacuation film demonstrating persistent contraction of terminal ileum with destruction of mucosal pattern.

he terminal ileum. The progress barium meal examination lso be done to demonstrate skip areas of involvement proximal

to a lesion previously demonstrated by barium enema. An initial plain film of the abdomen is often of value when the disease is complicated by obstruction. It will not differentiate this disease from other causes of intestinal obstruction.

ADDITIONAL AIDS IN DIAGNOSIS

A significant anemia of the microcytic hypochromic type was present in twenty patients in this series. The white blood count was elevated in only eleven instances. Stool examination may show the presence of pus, occult blood, or fatty acid crystals, but these findings are not diagnostic and are irregular in occurrence. Proctoscopic examination should be made in all cases to exclude the presence of coexistent ulcerative colitis. In some instances edema and/or small punctate ulcerations may be noted in the rectal mucosa. We believe that these findings may be secondary to the inflammatory changes in the ileum, either as a result of direct extension to the rectal wall which may be in close proximity to the loop of involved ileum, or of irritation of the rectal mucosa by purulent fecal contents.

DIFFERENTIAL DIAGNOSIS

Regional enteritis should be suspected in young adults complaining of persistent cramping abdominal pain, diarrhea and weight loss, particularly if they present a draining abdominal sinus or fistula-in-ano. Appendectomy has previously been performed in many of these cases. A palpable mass may be present in the right lower quadrant or pelvis. The diagnosis depends on positive roentgen findings. The diseases which may be confused most commonly with regional enteritis are (1) ulcerative colitis, (2) appendicitis, (3) intestinal tuberculosis, (4) tumors of the small bowel and (5) amebic granuloma. Ulcerative colitis can usually be differentiated with the aid of a proctoscope and an x-ray examination of the colon. Ordinarily the rectum and colon are primarily involved in ulcerative colitis.

Careful evaluation of the history is most important in differentiating the acute form of regional enteritis from appendicitis. The eliciting of mild antecedent symptoms of cramplike abdominal pain, weight loss and diarrhea will lead to careful roentgenologic examination and may establish the diagnosis. Unnecessary laparotomy for suspected appendicitis may thereby be avoided. A normal roentgenogram of the chest and negative stool examination for tubercle bacilli will usually exclude intestinal tuberculosis. If clinical signs and roentgen examination fail to differentiate this disease from a neoplasm of the small intestine, exploratory laparotomy is indicated. The positive finding of Endamoeba histolytica in the stools and a favorable response to amebic therapy will aid in differentiating regional enteritis from amebic granuloma.

TREATMENT

Although there is considerable controversy as to the management of this disease, the treatment which should be employed depends primarily upon the stage and extent of involvement and complications at the time the diagnosis is established. There is general agreement regarding the more conservative medical management of the acute forms of regional enteritis. It is in the chronic cases that authorities disagree upon the indication for surgery and on the merits of sidetracking operations with transection of the ileum versus resection of the diseased bowel. In the present series the disposition of these patients is shown in Table 3.

TABLE 3

MEDICAL AND SURGICAL RESULTS COMPARED

	Total	Satisfactory	Poor	Not Followed	Died
Treated medically	6	3	0	2	1
Treated surgically	49	25	12	6	6
Total	55	28	12	8	7

Medical.—Since the etiology of regional enteritis is unknown, there is no specific treatment. In the six patients treated medically the management included bed rest, high caloric, high protein, low residue diet, vitamin supplements, correction of anemia, and the use of various sulfonamide preparations. Four of the patients classified under medical treatment had exploratory laparotomy, at which time the diagnosis was confirmed and further surgical procedures were deemed inadvisable. One of these patients died of sepsis thirty days after operation. Three patients have made satisfactory progress on medical management. Sulfapyridine seemed to be of value in one case while phthalylsulfathiazole (sulfathalidine) appeared to be beneficial in another. Two patients have not been followed.

Surgical.[*]—The surgical treatment of these cases has been of two types. Twenty patients had sidetracking operations, including ileostomy and ileocolostomy, without transection of the bowel distal to the anastomosis. One patient had an ileotransverse colostomy with transection of the ileum. Thirty-five patients had resection of the diseased bowel. The results obtained by the sidetracking operation are shown in Table 4. In some of these cases, this operation was chosen because the surgeon believed the inflammatory process was too acute to perform an extensive resection safely.

Short-circuiting operations without transection of the bowel have not been satisfactory. The two patients classified as having good results have been in excellent health for three years and seven years.

[*] All operative procedures performed at the Cleveland Clinic were done by Dr. T. E. Jones or George Crile, Jr.

Of the twelve patients who were followed, ten did not improve. Seven subsequently had resection of the diseased bowel and are also included in Table 5 (resected group). Five of these patients improved after resection of the diseased bowel, one convalesced poorly because of persistent diarrhea, and one has not been followed. Of the three remaining patients classified as a poor result from the sidetracking operation, one has extensive segmental involvement of the jejunum

TABLE 4

RESULTS FOLLOWING SIDETRACKING OPERATIONS

	Total	Satisfactory	Poor	Not Followed	Died
Ileostomy	2		1		1
Ileocolostomy without transection of bowel	16	2	7	3	4
Ileocolostomy with transection	1		1		0
Entero-enterostomy	2		1		1
Total	21	2	10	3	6

and ileum and has required an entero-enterostomy on two occasions for partial intestinal obstruction. Another had an ileostomy done elsewhere. This patient was advised to have a resection of the diseased segment of ileum but declined and has had repeated hemorrhages from the ileostomy. The last patient had an ileocolostomy without transection of the ileum, performed elsewhere. Her disease is now inadequately controlled both clinically and roentgenologically.

TABLE 5

RESULTS FOLLOWING RESECTION OF DISEASED BOWEL

	Total	Satisfactory	Poor	Not Followed	Died
No. of patients	35	23	8	4	0

The patients classified as having had a resection include those in whom all obviously diseased bowel was completely removed. Necessary anastomotic procedures were carried out. Usually an ileotransverse colostomy was performed. In fifteen instances a two-stage procedure was employed, including the seven cases mentioned in the sidetracking group. There were no deaths immediately following operation in this group. The results of resection in thirty-five patients are shown in Table 5.

The twenty-three patients classified as having satisfactory results are all able to carry on their usual activities. Several of these patients have three or four loose stools per day at times. Roentgen examination has not revealed a recurrence of the disease. This tendency to diarrhea is no doubt due to shortening of the bowel with decreased absorptive area as a result of operation. In eight patients who had poor results, the disease was inadequately controlled in six following resection because of persistence of preoperative symptoms. Two patients had a recurrence of the disease, proved at operation nine and one-half and six years after initial resection.

COMMENT

The methods of treatment employed in the forty followed cases have accomplished satisfactory results in twenty-eight instances. Resection of all of the diseased bowel was most beneficial. Medical treatment may be tried in the acute or chronic mild cases without complications. Extensive segmental enteritis without complication may be treated better by conservative measures than by resection. With a prolonged follow-up period, recurrences will undoubtedly appear. Crohn[5] has reported a case in which there was a known recurrence twelve years after the initial operation and one of our patients had a recurrence nine and one-half years after the initial operation.

SUMMARY

1. The diagnosis and treatment of fifty-five patients with regional enteritis have been reviewed. Follow-up studies were made in forty of these cases.

2. Cramping abdominal pain, weight loss and diarrhea were the outstanding symptoms. The most common objective findings were a palpable mass usually located in the right lower quadrant of the abdomen, fever, a draining sinus of the abdominal wall, and/or a fistula-in-ano.

3. Confirmation of the diagnosis can be made only by roentgen examination or laparotomy.

4. Short-circuiting operations without transection of the bowel distal to the anastomosis and proximal to the diseased segment have proved an unsatisfactory method of treatment. Garlock and Crohn[5] report satisfactory results after sidetracking operations with exclusion of the diseased ileum.

5. A favorable percentage of patients treated by resection of the diseased bowel have made a satisfactory recovery during our observation period.

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ROENTGENOLOGIC DIAGNOSIS OF TUMORS OF THE LARGE INTESTINE

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The diagnosis of neoplasm of the colon depends on routine digital examination of the rectum, proctoscopic study, stool examination and roentgen visualization of the colon. By these means a functional disorder of the bowel can be differentiated from an organic lesion. Early diagnosis requires that these diagnostic studies be made in all cases presenting persistent symptoms referable to the bowel. Too frequently such investigation is deferred until metastases or other complications have occurred.

The importance of a detailed history and examination cannot be overemphasized. Symptoms should not be assumed to result from any suspected condition until definitely confirmed by examination. For example, hemorrhoids should not be assumed to be the source of rectal bleeding unless investigation establishes the diagnosis. A single diagnostic investigation does not preclude the possibility of neoplasm, and reexamination is indicated if clinical symptoms persist.

CLINICAL DIAGNOSIS

Malignant Lesions.—Carcinoma is the predominant malignant neoplasm of the large intestine. Sarcoma of the large intestine is relatively rare and cannot be differentiated from carcinoma with any degree of accuracy before operation. Carcinoma may involve any segment of the large intestine, but is found most frequently in the rectum and sigmoid colon. These lesions can occur in childhood, and it is not unusual to find them in the second and third decades. Occasionally multiple carcinomas are present, with sections of normal bowel between the lesions. Adenocarcinoma is the predominant type of carcinoma occurring in the colon. In the descending portion of the colon it usually produces an annular constricting deformity which causes symptoms of obstruction. In the ascending portion of the colon the adenocarcinoma usually develops as a polypoid irregular cauliflower-like growth that projects into the lumen of the bowel (Fig. 85 and 86). Obstructive symptoms are less likely to occur with the polypoid type of growth because the lesion does not encircle the bowel and because of the fluid state of the contents present in the proximal colon.

The clinical symptoms vary with the location of the lesion. The onset may be insidious and characterized entirely by a change in bowel habit. Dyspepsia, toxemia, anemia and weakness with loss in

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Fig. 85.—Roentgenogram of filled colon fails to demonstrate adequately lesion of ascending colon. See Fig. 86.

Fig. 86.—Spot films of the ascending colon (in Fig. 85) taken with patient rotated demonstrates large polypoid filling defect.

weight are the primary symptoms of carcinoma of the large intestine. A palpable mass is a late sign, but frequently some tenderness may be present over the lesion and, in the case of carcinoma of the cecum,

may lead to an erroneous diagnosis of appendicitis. Severe progressive anemia may be the only objective observation and may occur without any history of noticeable blood in the stools. Carcinoma of the large bowel on the right side must be considered in all cases of unexplained anemia. This is especially true of carcinoma of the ascending colon.

Obstruction of the large bowel on the right side is unusual except in cases of intussusception or involvement of the ileocecal valve.

In contrast to lesions of the ascending colon carcinoma of the descending colon tends to manifest itself by symptoms of obstruction. Colicky pain in proportion to the degree of obstruction is the rule. The closer the lesion is to the anus the more likely it is that a noticeable amount of blood will be present in the stool. The obstruction is usually chronic but may be acute, especially if the associated inflammatory change about the carcinoma is pronounced. The usual history is one of constipation alternating with diarrhea. Carcinoma of the transverse colon may simulate involvement of either the ascending or descending portion of the large intestine. This location should be suspected if a mass is present and movable, since the transverse segment is normally quite mobile.

It must be stressed, however, that carcinoma of the large intestine may not cause any symptoms referable to the bowel or that it may be masked by symptoms due to a lesion elsewhere, such as chronic cholelithiasis or peptic ulcer. In such cases the diagnosis depends on investigation of the colon as a part of more extensive studies. Occult blood will not be evident unless routine stool examinations are made; carcinoma of the rectum will continue to be mismanaged as long as digital and proctoscopic studies are deferred or omitted. The majority of rectal lesions cannot be diagnosed by examination with barium enema; x-ray visualization demonstrates lesions above the rectum and is not a substitute for proctoscopic study.

Benign Tumors.—Polyps are the most common benign tumors of the large intestine. Fibromas, myomas, lipomas, adenomas and angiomas have been reported but are uncommon. Tumors occurring extremely rarely are dermoids, teratomas and cysts. Differential diagnosis of these unusual neoplasms cannot be made accurately before operation.

Polyps may vary in number, size and location. They consist of a stalk and an epithelial layer continuous with the adjacent mucous membrane. The most important clinical significance of polyps is their tendency to undergo malignant degeneration. It is impossible to determine with certainty the time at which such change occurs; this may be evident only on microscopic examination. There is a definite familial predisposition to the development of this condition, especially of diffuse polyposis.

Polyps must be differentiated from so-called pseudopolyposis which accompanies ulcerative colitis. In this inflammatory condition the

"polyps" are represented by portions of mucosa uninvolved by ulceration. Bleeding from the rectum is the most common symptom of this condition and is due to erosion of the mucosa by fecal material. The pedunculated polyp is not infrequently associated with intussusception and may produce signs of obstruction. Seventy per cent of polyps occur in the rectum or sigmoid. According to Swinton and Warren[1] 14 per cent of their large series of carcinomas of the colon and rectum arose from benign mucosal polyps.

ROENTGEN DIAGNOSIS

Roentgen examination using the barium enema is the preferred method for visualization of the colon. This procedure should be preceded in all instances by digital and proctoscopic examinations in order to exclude neoplasm of the rectum. It is essential that the colon be cleansed before the barium enema is introduced in order to avoid confusing shadows on the film caused by fecal material. Unless contraindicated, castor oil (adults, 2 ounces) is given the night before the examination. Enemas should be avoided on the morning of the examination. Retained fluid and gas secondary to the enema renders this means of preparation much less satisfactory than castor oil. Proctoscopic study should be done the day before examination with the barium enema, as air retained following this procedure usually produces confusing shadows on the x-ray films.

The routine procedure for use of the barium enema is as follows: Barium is introduced rectally and the flow through the segments of the bowel controlled by fluoroscopic observation. The patient is rotated into each oblique position in order that redundant loops and flexures may be completely visualized. If the bowel is unusually redundant the overlapping of loops can occasionally be diminished by partially filling the bowel and allowing the patient to evacuate. The bowel will contract, and the barium enema may then be repeated. Administration of pitressin is a second means that may be employed to overcome redundancy. Under fluoroscopic control better visualization of a particular segment may be obtained with the patient in the prone position. By using an enema tip with a bulbous end no difficulty will be encountered in maneuvering the patient through these positions. Manual palpation is necessary to separate the loops and is of particular value in determining sites of tenderness and the presence of fixation.

At Cleveland Clinic routine spot films are made to demonstrate the sigmoid loop and ileocecal region. This practice has proved valuable, especially in the demonstration of early lesions that were not suspected during fluoroscopy. The spot film is the best means of recording and demonstrating any suspected area or lesion because it is made with the patient in the position most advantageous for this purpose. Redundant loops may obscure the lesion on the survey film. In all patients suspected of having a definite organic lesion in the large

bowel it is our practice to take films of the filled colon as well as of the evacuated bowel routinely. A roentgenogram of the filled colon is indispensable in the diagnosis of early ulcerative colitis. By fluoroscopic examination the slightly narrowed lumen could be considered due to spasm, and the minor serrations of the colon wall may be unnoticed due to lack of detail in the fluoroscopic image.

Early lesions may be demonstrated best on the evacuation film by changes in the mucosal pattern. All loops may be visualized on the film because of the contracted state of the bowel. The barium enema not only affords the best means of diagnosing an intrinsic lesion in the colon above the rectosigmoid area but also affords evidence of an extrinsic mass by the presence of pressure deformity or colon displacement. The study is not complete unless an air injection is done following evacuation of the barium. We perform this air study routinely if there is a history of bleeding from the rectum, if polyps are suspected, or if better visualization of a suspicious area or lesion is desired. Satisfactory air study depends on the adherence of a thin coating of barium to the bowel wall following evacuation of the barium enema. If air study is to be done later, filling of the terminal ileum with barium should be avoided, as loops of small bowel will then obscure the sigmoid area. Because of possible difficulties which may be encountered on roentgen visualization of the colon and because early lesions may not have caused sufficient change to establish a diagnosis, reexamination is indicated in every case having persistent symptoms before neoplasms can be excluded.

Examination of the large bowel using barium meal is less satisfactory than that using a barium enema. Tests with the meal are time-consuming and may require that films be made at twenty-four and seventy-two hour intervals before the site of the lesion can be determined. In addition, the presence of large bowel contents may cause bizarre and misleading deformities on the films. It is usually impossible to be certain of the constancy of the deformity and consequently of the certainty of a lesion. Barium given orally is contraindicated if obstruction of the large bowel is suspected, as this procedure can change chronic obstruction to acute and considerably complicate the problem. It is true, however, that the barium meal is useful in selected cases to determine the presence of a lesion about the ileocecal valve, especially when it is impossible to fill the ileum by retrograde barium or to be certain that the cecum is visualized.

Malignant Lesions.—The roentgen appearance of the lesion varies with the morphology of the growth. Carcinoma may be manifested as an obstructing lesion when a barium enema is used. Despite this apparent complete obstruction to retrograde barium, the clinical course may indicate that material passes through the site of the lesion from above. This may be due to the associated spasm initiated by the enema. Failure to visualize the extent and proximal margins of the

lesion makes a positive diagnosis of carcinoma by x-ray examination impossible, but this probability must be considered. If the barium passes proximal to the lesion the characteristics of the growth can be demonstrated. Early annular carcinoma may not be detected until evidence of infiltration of the wall and destruction of the mucosal pattern have developed. In its characteristic appearance this lesion will appear as an annular or napkin ring-like deformity involving a small segment of the bowel. The adjacent bowel is normal and the demarcating margins may be overhanging (Figs. 87 and 88).

In polypoid adenocarcinoma the tumor-like growth projecting into the lumen appears as an irregular filling defect with multiple or single areas of increased translucency. Invasion and erosion of walls may be

Fig. 87.

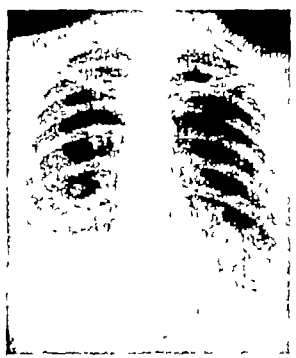

Fig. 88.

Fig. 87.—Typical napkin ring deformity of rectosigmoid colon.

Fig. 88.—Pulmonary metastasis from carcinoma of rectosigmoid colon in Fig. 87.

present, and ulceration of the tumor may be evident by the retained barium in the crater. This latter appearance is more likely to be seen on the evacuation film, which also affords more information on the degree of mucosal destruction and extent of the lesion. The roentgen appearance of carcinoma can be altered considerably by an associated inflammatory process, perforation, or formation of a fistulous tract. It is not unusual to have carcinoma associated with diverticulitis or diverticulosis (Fig. 89).

Carcinoma in ulcerative colitis is extremely difficult to differentiate from a defect due to an inflammatory mass. Neither the surgeon nor the pathologist can be positive in some cases from examination of the gross specimen alone. Differential diagnosis of lesions of the large intestine, such as tuberculosis, amebic dysentery, and appendiceal

Fig. 89.—Diverticulosis of sigmoid colon with annular filling defect due to carcinoma.

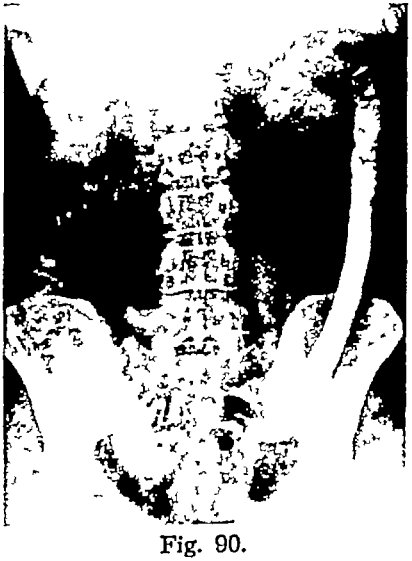

Fig. 90.

Fig 91.

Fig. 90.—Oval sharply outlined defect on evacuation film due to polyps of the sigmoid colon.

Fig. 91.—Large filling defect of transverse colon with intussusception caused by lipoma.

abscess, may be extremely difficult and depend on correlation with other clinical findings.

Benign Tumors.—Adequate preparation of the bowel is extremely important for the successful x-ray demonstration of benign tumors. These intraluminal tumors may not deform the contours of the bowel wall, and consequently the translucent defect can easily be confused with fecal material. These tumors do not cause destruction of the mucosal pattern or alteration of the haustral pattern. They are more likely to be shown on the evacution film when they will appear as sharply defined translucent defects (Fig. 90).

The filled colon may obscure such a lesion; therefore the air contrast study is essential to diagnosis in most cases. When polyps are suspected it is advisable to confirm their presence by reexamination. Intussusception is not infrequently caused by a benign tumor (Fig. 91), but the etiologic cause cannot usually be established before operation. Carcinoma cannot be excluded in such cases.

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the other hand, may be present for a considerable period of time before the mucosa is invaded and ulceration produced.

The age of the patient with neoplasm of the small intestine is a significant but not entirely dependable factor in diagnosis. The carcinoma group occurs more commonly in the fourth or fifth decades of life. In the sarcoma group the incidence is higher in the fourth decade, although it may occur at any time from infancy to advanced age.

ROENTGEN DIAGNOSIS

The roentgen examination is the most valuable procedure by which a definite diagnosis can be made. The examiner has the choice of three technics which may be used singly or in combination: (1) motility examination or interval study, in which the barium is given orally; (2) the so-called "small intestinal enema," in which duodenal intubation is employed with injection of a thin solution of barium through the tube; and (3) the standard barium enema, in which the success depends upon reflux of a sufficient amount of the solution through the ileocecal valve for visualization of the terminal ileum.

The oral administration of the barium solution will allow visualization of the entire length of the small intestine and is more satisfactory for lesions located in the proximal or midportions of the bowel. The barium enema is, as a rule, more satisfactory for demonstration of a lesion in the terminal portion of the small intestine. The duodenal intubation method has been used only occasionally in this Clinic, as we have found it to be somewhat difficult to obtain adequate visualization of the entire small intestine. This is due in part to the length of the bowel which is filled with the solution at one time, resulting in considerable overlapping of the intestinal loops.

Our usual procedure when a lesion of the small intestine is suspected is to employ first the interval study, and if that is negative, to follow with the barium enema. The latter, however, is not given until thorough cleansing preparation has eliminated any opaque material which may remain in the colon from the previous examination. The interval study may follow a set pattern, but a routine procedure cannot be established since the interval of viewing depends upon the time required for the passage of the opaque solution through the intestines. More frequent films or fluoroscopic examinations are made if any suspicious change is demonstrated. In all cases, however, we prefer to use a small amount of the barium mixture, generally not more than 2 ounces. This small amount allows adequate visualization and tends to avoid much of the overlapping loop shadows which occur if a larger amount of the mixture is given. The patient drinks the barium mixture in small sips during the initial fluoroscopic examination so that the proper amount may be determined. At this time careful examination of the esophagus, stomach, duodenum and proximal portion of the jejunum is made. "Spot" films are exposed immediately if any abnor-

mal changes are demonstrated. While it is true that the stomach is not filled with the barium mixture at the time of fluoroscopic examination, adequate visualization is usually obtained by demonstration of the mucosal pattern.

Following the initial fluoroscopic examination, survey films are exposed in the most appropriate position for demonstration of any changes noted. The study is then continued at intervals which may vary from minutes to hours, depending upon the rate at which the head of the meal passes to the intestine and also upon the discovery of any abnormal change that may be demonstrated. For this reason

Fig. 93.

Fig. 94.

Fig. 93.—Constricting filling defect of proximal ileum due to carcinoma. Tumor is obstructing, and there is moderate dilatation proximal to lesion.

Fig. 94.—Pronounced distention of ileum and loss of morphologic characteristic of tumor. Sudden onset from intussusception of a melanoma.

every examination of the small intestine is an individual problem and a definite routine method cannot be established.

The roentgen criteria for diagnosis of tumors of the small intestine are much the same as for the other portions of the gastrointestinal tract. The most important changes to look for are a localized deformity of the column of barium, which may manifest itself as a filling defect, an annular constriction or an infiltrative defect in the wall of the bowel. Although lesions other than tumors may simulate some of these changes, filling defects due to tumor are generally sharply demarcated at both the proximal and distal margins and involve a short segment. Other changes associated with tumor are alteration or obliteration of the mucosal pattern at the site of the lesion, obstruction and ulcera-

tion. Obstruction can develop slowly over a period of time and show an increasing degree of dilatation of the bowel extending in a proximal direction from the site of the lesion. In the early stage of obstruction, such as that produced by a constricting neoplasm (Fig. 93), the dilatation may not be pronounced and can be demonstrated for only a short distance proximal to the tumor. The obstruction and resulting dilatation may increase, however, to such a degree that the morphologic features of the lesion cannot be demonstrated by the roentgen examination (Fig. 94). The characteristic appearance of intestinal obstruction with severe dilatation, "step-ladder" pattern and multiple fluid levels is usually absent unless there be sudden onset such as that

Fig. 95.

Fig. 96.

Fig. 95.—Leiomyosarcoma of jejunum with ulcer crater. No obstruction and little alteration of mucosal pattern.

Fig. 96.—Infiltrating lymphosarcoma of duodenum. Note increased diameter of lumen and long segment involved.

introduced by intussusception of a polypoid tumor. This is due chiefly to the fact that the small intestine has the inherent ability to compensate for a gradual reduction in the diameter of the lumen.

One of the earliest manifestations of an intestinal tumor is alteration of the mucosal pattern. In the carcinoma group, which originates in the mucosa, this alteration will be the first change demonstrated in the roentgen examination. With the intramural type of lesion or in tumors arising outside of the lumen of the bowel, the early change in the mucosal pattern is due to pressure or stretching of the folds and may be slight. These changes are best demonstrated during the fluoroscopic examination and must be carefully sought throughout

the small intestine. As growth of the tumor progresses and size increases, the pattern may be entirely obliterated, even though the mucosa has not been invaded by the lesion. Ulceration will usually occur when the mucosa is invaded (Fig. 95) and may be the only roentgen evidence of a neoplasm which has developed external to the lumen of the bowel. In this case of leiomyosarcoma of the jejunum recently reported by Collins and Spencer[1] the mass of the tumor was external to the lumen, and obstruction was not present. Apart from the ulcer crater there was only slight alteration in the mucosal pattern and the lesion could easily have been overlooked had it not been for visualization of this crater.

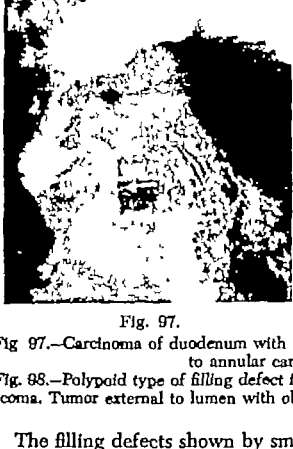

Fig. 97.

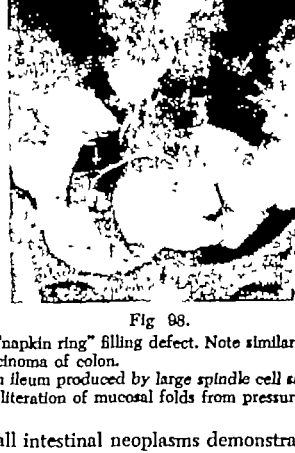

Fig 98.

Fig 97.—Carcinoma of duodenum with "napkin ring" filling defect. Note similarity to annular carcinoma of colon.

Fig. 98.—Polypoid type of filling defect in ileum produced by large spindle cell sarcoma. Tumor external to lumen with obliteration of mucosal folds from pressure.

The filling defects shown by small intestinal neoplasms demonstrate morphologic characteristics which place them in one of three general groups: the infiltrative defect, the annular or constricting defect, and the polypoid mass. It is possible, of course, to have a combination of these defects. The infiltrative defect occurs more commonly in tumors which are intramural in origin, of which lymphosarcoma (Fig. 96) is an example. These neoplasms may show involvement of a rather long segment of intestine, even when first discovered, and may resemble inflammatory changes in the roentgenogram Ulceration may or may not be present, as in many cases the mucosa will not be destroyed even though the infiltration is quite extensive.

Rigidity of the intestinal wall is apparent during the roentgen examination and especially prominent at the time of fluoroscopic procedure. It is during this phase of the examination that the lack of peristaltic movement through the involved segment is most striking. The lumen may show narrowing as well as infiltration but this change is not always present in neoplastic disease. The annular, constricting defect (Fig. 97) as highly suggestive of carcinoma, particularly if the appearance is that of a "napkin ring" deformity with involvement of a short segment. If possible, filling defects must always be differentiated from changes produced by an inflammatory process. In the latter condition the involved segment is usually longer than the one in neoplasm, and the limiting margins are not so sharply defined. Also, with inflammatory lesions there may be surrounding adhesions which are demonstrable by fixation of the bowel during fluoroscopic examination. With involvement of a short segment in inflammatory disease or a longer segment in the case of neoplasm, it may be impossible to make a definite diagnosis before operation.

Polypoid filling defects are, as a rule, well-defined negative shadows in the column of barium and are most often due to tumor of mucosal origin. However, neoplasms arising outside of the lumen may simulate this appearance by pressure or projection into the lumen of the bowel in the course of their development (Fig. 98). Benign tumors most frequently present a polypoid appearance, may be pedunculated, and at times are exceedingly difficult to differentiate from a malignant tumor.

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JAUNDICE

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THE term jaundice, regardless of the cause of the condition, denotes an increase in the blood bilirubin above the normal level with resulting pigmentation of the skin and sclerae. Serum bilirubin is measured specifically by the modified van den Bergh test in milligrams or units —1 mg. of bilirubin per 100 cubic centimeters of serum is usually considered equivalent to 2 van den Bergh units. The icterus index, although a simple method, is not a specific test for bilirubin, it is affected by slight hemolysis and by the presence of other pigments, such as carotene. However, an icterus index carefully done is often helpful and roughly parallels the van den Bergh reading, the ratio of icterus index to milligrams of bilirubin per 100 cubic centimeters varying from 5:1 to 10:1; with higher concentrations of serum bilirubin the ratio tends to be lower.[1] It is important not to mistake the yellow color of carotinemia, atabrine or other ingested pigments for jaundice: in these conditions the skin is pigmented but not the sclerae, the urine contains no bile, and the color of the stools is not changed.

Normal Bile Pigment Metabolism.—A clear knowledge of blood pigment metabolism is essential to an understanding of the different types of jaundice. Briefly, as illustrated in Figure 99, hemoglobin is normally broken down by the cells of the reticulo-endothelial system to a bilirubin which is nondialyzable, does not pass into the urine, and gives an indirect or definitely delayed direct van den Bergh reaction. Under normal circumstances this bilirubin is excreted by the liver so that its level in the blood usually does not exceed 0.5 mg. per 100 cc., having a total range of 0.2 to 1 mg. per 100 cc. In the liver, the bilirubin is modified† to a dialyzable form which gives a direct reaction with the diazo reagent and passes readily into the urine whenever, for any reason, it accumulates in the blood. After passage with the bile into the lumen of the intestines it is converted to urobilinogen, the oxidation product of which is urobilin (the pigment largely responsible for the color of the stool). A portion of the urobilinogen is absorbed from the bowel and carried to the liver in the portal blood

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† Possibly it is changed from a protein-bound bilirubin to a sodium salt.

to be almost entirely excreted in the bile by the undamaged liver, only minute amounts passing into the general circulation to be excreted in the urine.* Virtually all the urobilinogen is excreted in the stool; the total output, averaged over periods long enough to make up for the daily variation in size of stool, roughly parallels the rate of blood destruction.

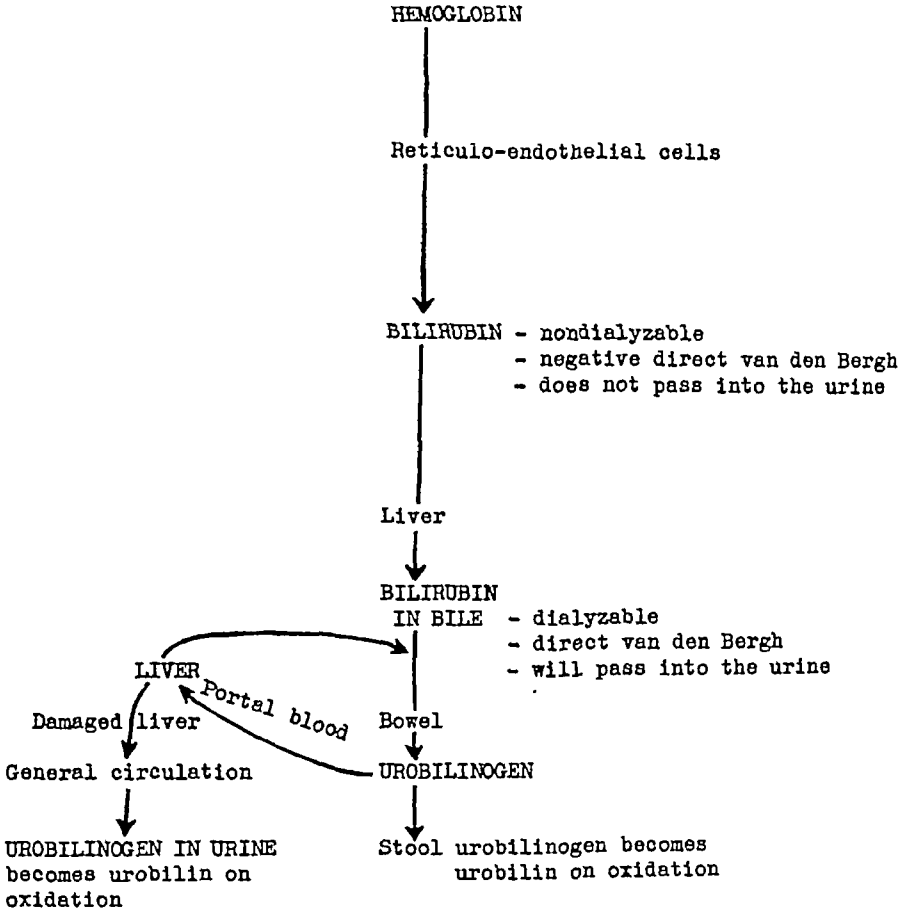

Fig. 99.

Abnormal Bile Pigment Metabolism.—Bile pigment metabolism is grossly altered in diffuse disease of the liver and in obstruction of the common bile duct, as well as in all conditions that affect the rate of blood destruction.

In *diffuse liver disease* disturbances in bile pigment metabolism vary with the stage and severity of the disorder. The earliest evidence

* Small quantities of urobilinogen may be detected with Ehrlich's reagent in a fresh specimen of normal urine. Rarely, however, will the test be positive in a dilution of 1:20. Normal urine subjected to the ordinary qualitative tests for urobilin, Schlesinger's, for example, will yield a negative or weakly positive test.

of hepatic dysfunction is the appearance of excess urobilinogen in the urine: the liver, slightly but diffusely damaged, allows the passage into the general circulation of abnormal amounts of urobilinogen which are then excreted by the kidney. A little greater damage begins to interfere with the excretion of bile by the liver. At first there is a damming back of the nondialyzable bilirubin which increases significantly in the plasma; this is often spoken of as retention jaundice. Soon there is difficulty in excreting even the pigment that has been modified by the liver and the more diffusible bilirubin begins to appear in the blood. By the time the jaundice becomes visible—at about the 2 mg. per 100 cc. level—there is enough of dialyzable fraction to give an immediate direct van den Bergh reaction and, from this time on, further increase in the serum bilirubin is largely due to the direct reacting fraction which, having been altered but not excreted by the damaged liver, is returned to the blood stream. In severe cases there is suppression of the excretion of bile and stools are clay-colored. The renal threshold for direct reacting bilirubin is low and it begins to be excreted in the urine at once. Renal clearance, however, is not adequate to excrete the large amount of pigment returned to the circulation and the bilirubin reaches a high level in the plasma, commonly varying between 10 and 20 mg. per 100 cc. When complete inability of the liver to excrete bile is associated with severe renal damage much higher serum levels are found, as for instance in some cases of Weil's disease when it may reach 30 to 40 mg. or more per 100 cc. As long as any appreciable amount of bilirubin passes into the intestine, much of the urobilinogen carried in the portal blood will pass through the damaged liver to the blood stream to be excreted in the urine in quantities far in excess of the normal. With complete suppression of the excretion of bile, urobilinogen will disappear from the urine.

The first change in jaundice due to *obstruction of the common bile duct* is an increase of the nondialyzable bilirubin in the plasma which is soon associated with an increase of the dialyzable fraction; for practical purposes, the plasma is found to give a direct reaction by the time the patient comes under observation. When the serum van den Bergh test is only slightly elevated, the direct reaction tends to be relatively stronger when the lesion is obstructive than when it is parenchymal; however this finding is not sufficiently constant to be useful as a differential test. When partial obstruction persists, the liver parenchyma becomes secondarily damaged and allows even reduced amounts of urobilinogen returning in the portal blood stream to pass into the general circulation and thence into the urine.

When there is *hemolysis or increased blood destruction*, the normal liver is often able to excrete the huge amounts of bile produced with little increase in the serum bilirubin—levels up to 1 to 2 mg. per 100 cc.—and without the appearance of excessive amounts of urobilinogen

in the urine. At times, however, the liver is unable to cope with the increased blood destruction; the serum bilirubin then may rise to levels ranging as high as 10 mg. per 100 cc., and considerable amounts of urobilinogen may appear in the urine. Similar findings are obtained after transfusion of blood of incompatible type: the foreign cells are rapidly hemolyzed and large quantities of bilirubin, that cannot be excreted by the liver in a short time, accumulate in the serum; but the jaundice is transient and the cause obvious.

CLASSIFICATION OF JAUNDICE

1. *Constitutional mild icterus.*
2. *Hemolytic icterus,* due to:
   - (*a*) Intravascular hemolysis,
     e.g.: mismatched transfusions, paroxysmal haemoglobinemias, malaria, blackwater fever, etc.
   - (*b*) Excessive breakdown of red cells by the reticulo-endothelial system,
     e.g.: congenital hemolytic icterus, sickle cell anemia, pernicious anemia, etc.
3. *Hepatic jaundice:*
   - (*a*) Diffuse disease of the liver parenchyma:
     - (1) Acute hepatitis due to virus infections,
       e.g.: sporadic hepatitis, epidemic hepatitis, homologous serum jaundice, yellow fever.
     - (2) Spirochaetal jaundice,
       e.g.: Weil's disease, syphilis.
     - (3) Toxic hepatitis,
       e.g.: (i) chemical toxins: chloroform, carbon tetrachloride, arsenic, trinitrotoluene, etc.
       (ii) bacterial toxins: septicaemias, typhoid, pneumonia, etc.
     - (4) Chronic hepatitis,
       commonly associated with splenomegaly and varying degrees of cirrhosis.
     - (5) Passive congestion.
   - (*b*) Obstruction of the large ducts:
     - (1) Intrinsic,
       e.g.: stone (cholangitis), stricture, parasites.
     - (2) Extrinsic,
       e.g.: (i) cancer involving head of the pancreas or adjacent structures.
       (ii) enlargement of lymph glands about the common bile duct—metatases, lymph gland disorders.
       (iii) abscess, inflammatory edema, etc., involving adjacent structures.

The above classification of jaundice will now be briefly discussed.

Constitutional Mild Icterus.—This is a benign disorder in which the serum bilirubin is slightly elevated, levels in any one case varying usually between 1 and 4 mg. per 100 cc. It has been described in the literature under such names as *constitutional hepatic dysfunction,*[2] *simple familial cholaemia,*[3] *icterus intermittens juvenilis,*[4] and *familial nonhemolytic jaundice.*[5]

This type of jaundice is almost symptomless; during periods of greater icterus there may, however, be increased ease of fatigue and listlessness. Frequently the disorder goes unrecognized. Its importance lies in the fact that physicians may note the jaundice and wrongly attribute it to disease of the liver, spleen or gallbladder. There may be a family history, but this is not essential to the diagnosis. Routine physical examination discloses only a slight icteric tint to the sclerae and skin in an otherwise normal individual. The spleen and liver are never enlarged.

Investigation will reveal a normal blood picture, fragility test and liver function. The direct van den Bergh reaction is negative even when the plasma bilirubin is increased to a level as high as 4 mg. per 100 cc. Ordinary qualitative tests for urobilin in the urine are commonly but not always negative. Stool urobilinogen has been reported as normal, low normal, or slightly increased.

As yet no satisfactory theory has been advanced in explanation of the liver's constitutional inability to clear the blood of bilirubin in a normal manner in these cases.

Hemolytic Icterus.—This term is applied to a group of disorders in which jaundice is produced either by intravascular hemolysis or by increased destruction of red blood cells by the reticulo-endothelial system. As a rule there is little difficulty in distinguishing either type from hepatic jaundice. Characteristically the jaundice is never severe, bile is not found in the urine, and the stools are deeply colored because of the increased excretion of urobilin. The immediate direct van den Bergh reaction is negative. Sooner or later anemia appears as the prominent symptom and overshadows the jaundice. Actually the jaundice may not be noted clinically.

(*a*) *Intravascular Hemolysis.*—The diagnosis of some of the types of intravascular hemolysis is obvious and does not require discussion (e.g.: mismatched transfusions, blackwater fever, etc.).

The group of hemolytic anemias, which includes all types of paroxysmal hemoglobinuria, is characterized more by refractory anemia and associated ill health than by jaundice. The diagnosis is often missed, partly because the jaundice is not noted.

(*b*) *Excessive Blood Destruction.*—Familial hemolytic icterus is the only disease manifested by increased blood destruction with which we need be concerned in this discussion; conditions such as sickle cell anemia and pernicious anemia are identified as specific anemias, with mild jaundice playing an insignificant or secondary role.

In familial hemolytic icterus the fundamental defect appears to be an abnormality of the red blood cells which are characteristically spherical and exhibit decreased resistance to hypotonic saline solutions. These spherocytes are readily destroyed by the spleen. The disease is characterized by hemolytic crises superimposed on a persistently increased rate of blood de[illegible]

anemia are early manifestations usually first noted in adolescence. In crises of increased destruction, malaise, fever, nausea and vomiting may be prominent features; jaundice becomes deeper and anemia may be severe. Between crises the anemia, mild jaundice and splenomegaly persist and tend to become gradually more marked. The diagnosis is usually obvious on clinical grounds; it is confirmed by recognition of the spherocytosis and the abnormal fragility test. Even when a family history is not evident, examination of other members of the family may disclose splenomegaly and spherocytosis in the absence of definite symptoms.

The most constant change in pigment metabolism is a greatly increased output of urobilinogen. The level of plasma bilirubin is extremely variable, being dependent not only on the rate of blood destruction but also on the ability of the liver to excrete excessive amounts. Even when the serum bilirubin is but little elevated the urobilinogen output in the stool is increased many times.

On removal of the spleen, the increased breakdown of red cells usually ceases although spherocytosis and abnormal fragility of the red cells persist; changes in the pigment metabolism are dramatic; the serum bilirubin falls to a normal level; urobilinogen disappears from the urine and its output in the stool becomes normal.

Pigment stones, which are almost always present in cases of congenital hemolytic icterus, occasionally may give rise to biliary colic and obstructive jaundice. This fact makes the careful differentiation of the type of jaundice in such cases extremely important.

The term *acquired hemolytic icterus* is often applied to a miscellaneous group of cases which display mild jaundice and increased excretion of urobilin but are not familial and usually lack the typical blood changes, such as spherocytosis or increased fragility. Cases of intravascular hemolysis are sometimes wrongly included in this group. The picture is not sufficiently definite to warrant further consideration in this discussion.

Hepatic Jaundice.—The term hepatic jaundice is used here to designate all those conditions in which jaundice occurs as a result of diffuse disease of the liver parenchyma or obstruction of the large bile ducts. When jaundice is visible, the serum van den Bergh gives a direct reaction and bile is found in the urine; at lower levels, especially at the onset, the unmodified bilirubin may account for a latent jaundice before the direct-reacting bilirubin increases significantly.

The therapeutic importance of distinguishing jaundice due to disease of the liver parenchyma from that caused by obstruction of the common bile duct cannot be overemphasized. All age groups are subject to either type, but infective hepatitis is more prone to occur in the younger age groups and obstructive jaundice in the later decades. In either type the jaundice may be mild or severe; it may be transient or of long duration. Pruritus becomes a prominent symptom in most

long-standing cases in both groups. When either of these types of jaundice is prolonged, the color of the skin slowly changes from the early golden yellow to a later dark grayish, yellow-green. In both, the fecal output of urobilinogen is diminished to varying degrees, clay-colored stools being the rule in severe cases; most complete obstruction, however, occurs in cases of carcinoma of the head of the pancreas when, at most, only a few milligrams of urobilin can be demonstrated in the stool. Long-standing, severe jaundice of either type may lead to vitamin K deficiency but this is more common, and of greater immediate importance, in cases of obstructive jaundice where surgical measures may be undertaken. Changes in serum proteins may occur: mild in acute diffuse diseases of the liver; striking in chronic hepatitis; but in obstructive jaundice only after the liver parenchyma has been damaged as a result of prolonged back pressure. Certain differential liver function tests are helpful at times, but no one test or combination of tests is constantly dependable. In the majority of cases the differentiation can be made on the clinical manifestations which will now be described.

(*a*) *Jaundice Due to Diffuse Disease of the Liver Parenchyma.*—Whether the diffuse liver damage be the result of infection, as in the various forms of acute hepatitis, or due to chemical or bacterial toxins, marked anorexia is a prominent, early and almost constant symptom. It is always present at the beginning in acute cases but occasionally may be lacking in low grade liver disease of gradual onset. Associated with the anorexia are malaise, weakness, fatigue and, in the more severe cases, nausea and vomiting. In hepatic damage of infectious origin there often is a short febrile period when the infection may be generalized, and during which time the anorexia and associated train of symptoms appear. After a period of a few days mild jaundice is noted, urobilin and bile are found in the urine, and the jaundice rapidly becomes more severe. In atypical, prolonged hepatitis the onset may have been inconspicuous and the anorexia mild; if the patient be past middle life, differentiation from obstruction caused by carcinoma of the head of the pancreas may then be difficult.

When the hepatic damage is caused by chemicals, such as chloroform, carbon tetrachloride, phosphorus, trinitrotoluene, and the like, or by potentially toxic drugs, the rapidity of onset varies with the degree of exposure, amount ingested and the susceptibility of the person. It may be either rapid or very gradual. In all severe cases anorexia is a prominent early symptom and, even in the most acute cases, it precedes the appearance of the jaundice by from one to four days. The duration of the jaundice also varies greatly: it may be evanescent, as after mild overdosage of chloroform or carbon tetrachloride, or of long duration, as in severe trinitrotoluene poisoning. The importance of a history of administration of potentially toxic drugs, such as arsenic, gold, sulfonamides or cinchophen, or of ex-

large amounts of urobilin are found in the urine; the appetite may improve for a time, and there may be a temporary gain in weight of many pounds.

LIVER FUNCTION TESTS

Certain differential liver function tests may help in the diagnosis of doubtful cases. However, as noted previously, these tests are not consistently dependable and must be carefully related to the clinical picture.

The *cephalin-cholesterol flocculation test*° is so sensitive that a weakly positive result has little significance. A strongly positive test is indicative of diffuse liver damage. In the presence of jaundice, a negative result favors the diagnosis of obstruction of the common bile duct.

The *galactose tolerance test* is positive in most cases of deep jaundice due to disease of the liver parenchyma. Many exceptions have been noted however, and a negative result is not indicative of obstruction.

The *plasma alkaline phosphatase* is definitely increased in obstructive jaundice and the high level persists until the jaundice has largely subsided. It may be slightly or moderately raised in diffuse hepatic disease. Sufficient overlapping occurs in the two types to render a moderate increase of no differential value. In the presence of jaundice, normal or slightly elevated levels in repeated tests virtually rule out the diagnosis of obstruction of the large bile ducts.

Increase in the serum globulin and the appearance of *abnormal globulin fractions* have been noted in long-continued disease of the liver parenchyma. Alterations of mild degree may occur in acute hepatitis. In jaundice of long standing, gross and persistent changes are indicative of chronic diffuse hepatic disease.

REMARKS

The differentiation of the type of jaundice depends largely on clinical manifestations and little difficulty is encountered in the majority of cases. In some instances, however, a period of observation is required and certain differential liver function tests are helpful.

Low grade hepatitis of gradual onset occurring in older people may be confused for a time with carcinoma of the head of the pancreas or related structures, particularly if the usual initial period of anorexia and malaise has been mild, lacking or not remembered. The course of the disease will usually make the diagnosis obvious within a month, but occasionally deep jaundice persists for a longer period. The cephalin-cholesterol flocculation test is almost always strongly positive; the galactose tolerance test may be definitely positive and is then of value, but in less acute cases it is often negative; if the alkaline

° Other similar reactions, such as the thymol turbidity test, give comparable findings.

phosphatase be moderately raised it is not differential, but normal or slightly increased readings point to the correct diagnosis.

Persistent jaundice due to stone fixed at the ampulla of Vater may be confused with jaundice due to obstruction by carcinoma of the head of the pancreas or even with prolonged hepatitis. The actual onset of the jaundice may have been painless but almost invariably there is a history of previous attacks of biliary colic. The latter fact usually clarifies the issue. The liver function tests are clearly those of obstructive jaundice unless there have been previous attacks of cholangitis.

The diagnosis of icterus due to cholangitis is usually obvious because of the repeated attacks of pain and jaundice often associated with fever and chills; if due to stricture, there is usually a history of a stone or of a former operation on the biliary tract. Differential function tests are commonly confusing because the obstructive jaundice is associated with severe secondary parenchymal damage. The cephalin-cholesterol flocculation and galactose tolerance tests may both be positive while the serum alkaline phosphatase is greatly increased.

Biliary cirrhosis may be secondary to prolonged cholangitis from stone or stricture; the diagnosis is then clear. Primary biliary cirrhosis is seldom diagnosed in the early stages. At first it may be confused with acute hepatitis. When jaundice persists for a long time, sometimes fluctuating, the question of stone or carcinoma is raised. There is no history of biliary colic but fever and epigastric distress may be present, particularly in relapses, with deeper jaundice. The liver and spleen become progressively larger. The serum alkaline phosphatase is greatly increased, and the cephalin-cholesterol flocculation and galactose tolerance tests usually give normal results. Exploration of the abdomen is sometimes undertaken to rule out stone and establish the diagnosis by biopsy.

It is notable that jaundice is rarely caused by local lesions, such as single or multiple metastases, abscess of the liver or amebic hepatitis, even when the lesions are very extensive. The liver may be greatly enlarged by widespread, secondary new growth without interference with the excretion of bilirubin unless there is compression of the ducts at the porta hepatis. Relatively rarely is even a mild or latent icterus demonstrated. Similarly, the miliary abscesses of pylephlebitis seldom cause deep jaundice although a mild icterus, often transient, may occur. Deep jaundice is found only when there is diffuse damage to all the liver cells or obstruction of the common bile duct.

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SERUM PROTEINS IN HEPATIC DISEASE

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INTRODUCTION

THAT marked abnormalities of the serum proteins may occur in patients suffering from various disturbances of the liver has been known since 1907 when Gilbert and Chiray[1] observed that in patients who had cirrhosis and ascites there frequently was a fall in the level of the total blood proteins. In the same year Grenet[2] pointed out that this decrease particularly involved the albumin portion of the serum and, in 1922, Filinski[3] drew attention to the increase in serum globulin found in patients with various forms of hepatic insufficiency. In 1929, Abrami and Wallich[4] published the results of fractionation of the serum proteins in a series of cases of Laennec's cirrhosis, all of which showed a fall in the serum albumin and varying increase in the serum globulin resulting in a marked decrease in the albumin-globulin ratio. Since that time many investigators[5] have confirmed and extended these observations.

During the years immediately before World War II we began to be interested in the serum proteins, particularly in the globulin fractions that were to be found in a wide variety of diseases.[6] This interest was greatly helped by the development, by Campbell and Hanna,[7] of an improved and more rapid salting-out technic, using sodium sulfite, for the separation of these protein fractions. This technic not only separates the serum proteins into the recognized fractions, albumin, pseudoglobulin and euglobulin, but it also allows the recognition in certain cases of the presence of an abnormal fraction—probably a globulin. This abnormal globulin, which is not present in normal serum, is precipitated by 13½ per cent sodium sulfite. This is a fraction in which we have been particularly interested and, for lack of a better name, it will be referred to as the "13½ per cent fraction."

This rapid method of separating the various fractions combined with the more powerful Kjeldahl digestion mixture devised by Campbell and Hanna[8] has made the determinations of the serum protein fractions much less laborious and has permitted such determinations

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to be done on a wide variety of patients. These fractions, of course, are not true chemical entities. They are simply fractions which are separated one from the other by their different solubilities in varying concentrations of sodium sulfite. Because the proportions of these fractions vary from normal in a characteristic way in certain illnesses, and particularly in hepatic disease, we have found such determinations helpful in the diagnosis of chronic disease of the liver and in following the course of recovery of the more acute cases. We consider that the actual amounts of these fractions may be more significant than the empirical reactions, such as the Takata-Ara reaction,[9] the cephalin-cholesterol flocculation test,[10] the thymol turbidity test,[11] and the formol-gel test,[12] which depend in some measure at least upon alterations in the relative amounts and character of the serum protein fractions.[13]

SERUM PROTEINS AND THEIR FRACTIONS IN NORMAL INDIVIDUALS

In Table 1 are given the maximal variations of the serum proteins and their fractions, as bound by the sulfite technic, in forty young adults. It will be seen that these fractions show a fair degree of con-

TABLE 1

SERUM PROTEINS IN FORTY NORMAL INDIVIDUALS*

	Serum Protein† (gm./100 cc.)					
	Total Protein	Albumin Fraction	Total Globulin Fraction	Pseudo-globulin I and II	Euglobulin Fraction	13½% Fraction
Males	6.88	5.00	1.88	1.14	0.74	0
Females	6.95	4.96	1.98	1.15	0.84	0
Maximum	7.80	5.70	2.50	1.50	1.00	0
Minimum	6.20	4.00	1.64	0.90	0.60	0
Average	6.91	4.98	1.93	1.14	0.79	0

* Adapted from Campbell et al., 1942.[6]

† The protein values in this and in subsequent tables are corrected for nonprotein nitrogen.

stancy. The average value of the serum albumin is 5 gm. per 100 cc., and of the serum globulin just under 2 gm. per 100 cc. These values compare favorably with those given by Wiener and Wiener,[5b] Peters and Eisenman,[5c] and others who have used the Howe sodium sulfate technic.[14] The globulin fractions known as pseudoglobulin I and pseudoglobulin II are combined in the table and amount to just over 1.1 per cent. The euglobulin fraction varies between 0.6 and 1 per cent, with an average value of 0.79 per cent. It tends to be higher in females than males, a finding previously noted by Salvesen.[5a] In none

was there evidence of any appreciable precipitation by 13½ per cent sodium sulfite. We have taken this fraction to be absent when no obvious precipitate appears in the ten minute period allowed. At times, if the filtration is carried through even when the mixture appears to be clear, a small proportion of protein seems to be removed. This should never exceed an amount corresponding to 0.2 to 0.3 gm. of protein per 100 cc., an amount which is not regarded as significant.

SERUM PROTEIN FRACTIONATION IN PATIENTS WITH HEPATIC DISEASE

Fractionation of the serum proteins of a large number of patients with various types of hepatic disease has been carried out. In all cases the proteins have been separated into their albumin and globulin fractions and a qualitative test has been done with 13½ per cent sodium sulfite. When this qualitative test for the abnormal fraction was found to be positive, the actual amount was determined by the Kjeldahl method. When it is not feasible to determine this quantitatively, the qualitative result can be recorded in degrees of turbidity. Because it has been noted that the abnormalities in the serum proteins of patients with hepatic disease have occurred in the euglobulin rather than in the pseudoglobulin fractions, we have not, as a general rule, estimated the pseudoglobulins I and II separately. Also, unless the total globulin has been found to be 3 gm. or more per 100 cc. or a positive result has been obtained for the "13½ per cent fraction," we have not always separated the serum globulin into its various fractions.

Acute Infective Hepatitis.—Shortly after the onset of the disease, patients with acute infective hepatitis of no more than the usual severity have not shown any gross abnormality of the total serum proteins. However, a mild decrease in the serum albumin and a definite increase in the level of the total globulin does occur in almost all cases. This occurs largely as a result of an increase in the euglobulin fraction which may rise to more than double its normal value. There is a slight increase in the pseudoglobulin fraction as well and in a small proportion of cases a definite amount of the "13½ per cent fraction" has been found. The initial values found in a number of patients are given in Table 2. These determinations were all made within a day or two of the arrival of the patient on the ward but, as can be seen from the duration of the illness (based upon the clinical history), some of them had been unwell for as long as a month or more before admission to hospital. All of the patients reported in this table, with the possible exception of Case 5, recovered completely and are considered to have had acute infective hepatitis.

The serum of these patients was examined several times during the course of the illness and after recovery. Many showed no more than a mild increase in the euglobulin fraction at any time and never showed

any evidence of the presence of the "13½ per cent fraction." A number, however, who showed relatively normal values at the time of admission did develop definite abnormalities in the euglobulin and "13½ per cent fraction" during the course of their illness. In these, as well as in the patients who showed such abnormalities at the onset, recovery was accompanied by a return to approximately normal values. This is illustrated by the data in Table 3.

TABLE 2

ACUTE INFECTIVE HEPATITIS: SERUM PROTEIN VALUES ON ADMISSION TO THE MEDICAL SERVICE

Case No.	Days Since Onset	van den Bergh (units)	Serum Proteins (gm./100 cc.)					
			Total	Albumin Fraction	Total Globulins	Pseudo-globulin Fraction	Total Euglob-ulin Fraction	13' % Fraction*
1	11	12.5	7.0	4.2	2.8	...	...	0
2	9	11.0	7.2	4.3	2.9	1.4	1.5	0.5
3	9	9.6	7.1	4.2	2.9	...	...	0
4	42	26.7	6.3	4.0	2.3	...	...	0
5	9	9.3	†5.4	3.6	1.8	...	...	0
6	14	15.6	7.0	3.8	3.2	1.3	1.9	1.0
7	10	13.6	6.4	4.1	2.3	...	...	0
8	8	9.3	7.3	4.6	2.7	...	...	0
9	8	6.0	6.7	4.3	2.4	...	...	0
10	9	13.4	6.2	3.2	3.0	1.3	1.7	0.8
11	5	4.4	6.6	3.6	3.0	1.3	1.7	0.8
12			6.3	4.3	2.0	...	...	0
13	10	9.0	6.3	4.4	1.9	...	...	0
14	23	8.6	6.7	4.6	2.1	...	...	0
15	30	5.2	6.8	4.0	2.8	...	...	0
Maximum			7.3	4.6	3.2			1.0
Minimum			5.4	3.2	1.8			0.0
Average			6.62	4.08	2.54			
Normal			6.9	5.0	1.9			

* It is to be noted in this table, and in subsequent ones, that the 13½% fraction, when present, is included in the total euglobulin fraction.

† This patient has been receiving, just prior to observation, intravenous glucose and saline solution because of vomiting.

The data presented for Case 5 show that a considerable rise in the serum globulins occurred during the course of the illness, which did not reach a maximum until some months after apparent clinical recovery. This rise in the total serum globulins was associated with an increase in the euglobulin and the appearance of an appreciable amount of the "13½ per cent fraction." These findings suggest, in the light of the data to be presented in connection with cirrhosis, that this patient had a degree of chronic hepatitis, a suggestion supported by

the persistent mild elevation of the serum van den Bergh and by the fact that five months after the onset her spleen became palpable for the first time. At this time a bromsulfalein test showed 7 per cent retention after half an hour—a result slightly but definitely higher than normal Unfortunately, after her last appearance in November, 1946, the patient moved from the city and no further examinations have been possible

TABLE 3

SERUM PROTEIN VALUES DURING THE COURSE OF ACUTE INFECTIVE HEPATITIS

Case No	Days Since Onset	Van den Bergh (units)	Serum Proteins (gm /100 cc.)					
			Total	Albumin Fraction	Total Globulin Fraction	Pseudo-globulin Fraction	Total Euglob-ulin Fraction	13½% Fraction
Normal			6 9	5 0	1 9	1 1	0 8	0
13	10	9 0	6 3	4 4	1 9			0
	19	1 8	6 7	4 4	2 3			0
	51	0 4	6 7	4 8	1 9			0
	93	0 3	7 1	5 3	1 8			0
8	8	9 3	7 3	4 6	2 7			0
	32	23 2	7 7	4 8	2 9			0
	46	5 0	7 8	4 8	3 0	1 3	1 7	0 6
	61	1 7	7 3	4 9	2 4			0
	74	0 9	7 4	5 1	2 3			0
2	9	11 0	7 2	4 3	2 9	1 5	1 4	0 5
	30	1 0	7 1	4 2	2 9	1 4	1 5	0 7
	48	0 6	7 3	4 7	2 6	1 3	1 3	0 5
	70	0 5	7 0	4 6	2 4			0
5	9	9 3	5 4	3 6	1 8			0
	34	1 2	7 8	4 8	3 0	1 4	1 6	0 8
	56	1 5	8 0	4 8	3 2	1 5	1 7	0 7
	84	1 5	7 5	4 5	3 0	1 4	1 6	0 7
	118	1 8	8 2	4 6	3 6	1 5	2 1	1 1
	153	2 2	7 8	4 5	3 3	1 3	2 0	1 0
	181	2 4	7 4	4 3	3 1	1 1	2 0	0 6
	279	3 1	6 7	3 8	2 9			0
	335	1 8	6 7	4 7	2 0	1 2	0 8	0 4

Weil's Disease.—The serum proteins have been followed in two cases of Weil's disease, in both of which the patients recovered In one case the serum proteins were relatively normal throughout the illness except for a mild decrease in the level of the serum albumin In the other a gradual rise in the serum globulins occurred, reaching 3 8 gm per 100 cc. about five weeks after the onset at a time when the jaundice had almost entirely disappeared At this time the "13½ per cent fraction" was 1 gm per 100 cc This gradually decreased until it

disappeared almost two months later, and the euglobulin fraction also became more normal.

Acute Necrosis of the Liver.—In one case of acute necrosis of the liver (coming on suddenly in a patient who had been ill for three weeks before admission with what was felt by his family physician to be acute infective hepatitis), the serum albumin was found to be reduced to 2.3 gm. per 100 cc. and the total globulin fraction was

TABLE 4

SERUM PROTEINS IN LAENNEC'S CIRRHOSIS

Case No.	Serum van den Bergh (units)	Serum Proteins (gm./100 cc.)					
		Total	Albumin Fraction	Total Globulin Fraction	Pseudo-globulin Fraction	Total Euglobulin Fraction	13½% Fraction*
1	0.6	6.8	2.7	4.1	1.7	2.4	1.4
2	0.5	7.5	2.6	4.9	1.4	3.5	2.5
3	0.6	8.6	3.8	4.8	1.6	3.2	2.0
4	0.6	6.0	3.0	3.0	1.2	1.8	0.8
5	2.0	5.9	2.9	3.0	1.1	1.9	1.0
6	8.0	6.0	2.6	3.4	1.5	1.9	0.9
7	1.2	6.3	2.9	3.4	1.2	2.2	1.2
8	4.8	7.0	3.2	3.8	1.6	2.2	1.0
9	0.4	9.0	5.4	3.6	1.6	2.0	0.9
10	1.5	8.1	4.6	3.5	1.5	2.0	0.9
11	2.5	5.7	3.1	2.6	...	...	0
12	1.8	9.3	3.2	6.1	1.6	4.5	2.5
13	1.0	5.3	2.7	2.6	...	...	0
14	0.5	6.0	2.8	3.2	1.2	2.0	1.1
15	8.6	7.5	3.0	4.5	1.4	3.1	2.1
16	4.0	8.0	3.7	4.3	2.3	2.0	0.6
17	4.0	6.3	2.5	3.8	1.5	2.3	1.2
18	0.9	6.8	2.7	4.1	1.7	2.4	1.5
19	1.8	5.8	3.0	2.8	...	...	0
20	...	6.4	3.0	3.4	1.5	1.9	1.1
Maximum		9.3	5.4	6.1	2.3	4.5	2.5
Minimum		5.3	2.5	2.6	1.1	1.8	0
Average		6.9	3.2	3.7	1.5	2.4	1.2
Normal		6.9	5.0	1.9	1.1	0.8	0

* See Table II, footnote.

elevated to 3.60 gm. per 100 cc. Of the globulin fraction 2.4 gm. per 100 cc. was euglobulin and 1.3 gm. per 100 cc. was precipitated by 13½ per cent sodium sulfite. These values did not alter materially during the few days that the patient was in hospital preceding his death.

Chronic Hepatitis (Cirrhosis).—1. *Laennec's Cirrhosis.*—The results of fractionation of the serum proteins in twenty cases of Laennec's cirrhosis are given in Table 4. It is evident that marked changes

in the serum proteins are shown in every case. The characteristic finding is a well marked increase in the serum globulins to levels that may reach three times the normal value, accompanied by a more or less corresponding fall in the serum albumin. The euglobulin fraction is considerably increased in most cases—in one case, *up to five times* the normal value—and in all but three cases an appreciable amount of the "13½ per cent fraction" has been found.

In three cases, No. 11, 13 and 19, the total globulins were only slightly raised and the "13½ per cent fraction" was absent. These findings were confirmed on several examinations. All three patients were exceedingly malnourished, were in the terminal stages of cirrhosis and required numerous abdominal paracenteses for the relief of ascites. In Case 11, the results found during the last stage of the illness are given in Table 5. The main abnormality found in the serum

TABLE 5

SERUM PROTEINS IN TERMINAL LAENNEC'S CIRRHOSIS

Case No.	Date (1946)	Serum van den Bergh (units)	Serum Proteins (gm./100 cc.)			
			Total	Albumin Fraction	Globulin Fraction	13½% Fraction
11	May 8		5.7	3.1	2.6	...
	May 28	2.5	5.3	3.0	2.3	0
	June 7	1 6	5 0	3.2	1.8	0
	June 18	1.3	4.5	2.5	2.0	0
	June 25	1.8	4.2	2.2	2.0	0
	June 30	Patient died.				

Autopsy: Portal cirrhosis with small (1280 gm.), hobnailed liver.

proteins is the marked decrease in the serum albumin, probably accounted for by hepatic failure and the great loss of protein resulting from repeated paracenteses in this case.

All of the patients recorded in Table 4 were treated with a high protein, high caloric diet with added brewers' yeast, and all had repeated examinations of their serum proteins. In a few cases there was an increase in the serum albumin during the high protein regime with improvement in the clinical condition, but in many more there was not any striking change either in the albumin or globulin or in the abnormal "13½ per cent fraction." In Table 6 are given the details of the repeated examinations of four such patients.

In Case 6 the patient, a severe chronic alcoholic, was admitted after an episode of particularly heavy drinking with marked jaundice and a large, fatty liver with ascites. While in the hospital, his jaundice and

ascites disappeared and his serum albumin rose from low to normal values without much change in the globulin level. Shortly after discharge from the hospital this patient resumed his drinking habits and was readmitted in a severe relapse which caused his death. The serum proteins, during this second admission, showed once more a sharp de-

TABLE 6

SERUM PROTEINS DURING THE COURSE OF LAENNEC'S CIRRHOSIS

Case No.	Date	Serum van den Bergh (units)	Serum Proteins (gm./100 cc.) Total	Albumin Fraction	Globulin Fraction	13¼% Fraction	Remarks
6	11/3/46	8.0	6.0	2.6	3.4	0.9	Alcoholic. Admitted after prolonged excess.
	2/4/46	2.3	6.6	2.8	3.8	1.4	In hospital. Improving clinically.
	7/6/46	0.6	8.3	4.8	3.5	0.8	Discharged on high protein diet.
	20/7/46	11.2	6.8	2.4	4.4	1.0	Readmitted in relapse following alcoholic excess. Died.
8	3/4/46	4.8	7.0	3.2	3.8	1.0	Admitted. Typical history of chronic alcoholism. Large liver; ascites. Paracentesis necessary twice.
	16/4/46	2.4	6.8	3.5	3.3	0.5	In hospital: on high protein diet; improving.
	5/6/46	1.0	7.6	4.3	3.3	0.4	Discharged. Ascites diminished. No need to do paracentesis.
	18/3/47	0.3	7.4	4.2	3.2	0.5	Readmitted. Beginning to drink again.
	12/5/47	0.4	8.3	5.1	3.2	0.7	In hospital; on high protein diet.
	28/6/47	0.4	8.3	5.0	3.3	0.8	Carrying on at home on high protein diet.
	8/9/47	0.4	7.4	4.4	3.0	0	Outpatient visit. Doing well. Ascites cannot be demonstrated.
9	29/4/46	0.4	9.0	5.4	3.6	0.9	Nonalcoholic. Admitted because of excessive vaginal bleeding. Gross enlargement of liver and spleen. No ascites.
	9/11/46	0.4	8.8	4.7	4.1	0.8	Outpatient visit. On high protein diet. No further bleeding.
	19/5/47	0.4	8.4	4.6	3.8	0.7	No further haemorrhage.
	15/9/47	0.4	8.8	4.4	4.4	1.8	Feels well. No change in liver; spleen a little larger.
14	2/10/46	1.0	6.0	2.8	3.2	1.1	Nonalcoholic. Large liver discovered on discharge from Army; no ascites.
	20/12/46	1.7	6.0	3.1	2.9	0.6	On high protein diet and added yeast.
	4/3/47	....	6.1	3.4	2.7	0.6	Placed on choline, 4 gm. daily.
	18/6/47	....	6.0	2.8	3.2	1.0	Feels reasonably well Choline continued.
	16/10/47	....	6.6	3.0	3.6	1.4	Choline stopped. Feels reasonably well. No edema or ascites. No change in size of liver or spleen.

crease in the serum albumin and a still further rise in the serum globulin.

The patient of Case 8, who had a typical history of chronic alcoholism, was admitted to hospital with jaundice, enlarged liver and ascites. With a high protein diet his serum albumin has risen to normal levels and the ascites has disappeared. There has been little change in the size of his liver. Patients 9 and 14 are living and in reasonably good

health. Patient No. 14 does have some mild edema of his feet when up and about all day but patient No. 9, whose serum albumin is normal, has no such complaint. Neither of these patients has any history of alcoholism; both have grossly enlarged livers which have shown very little change during the period of observation, and patient No. 14 has not shown any significant change in symptoms or findings during the six months that he has been receiving 4 gm. of choline hydrochloride daily.

The values found for these various protein fractions in normal individuals, in cases of acute infective hepatitis and in cases of portal cirrhosis are graphically compared in Figure 100.

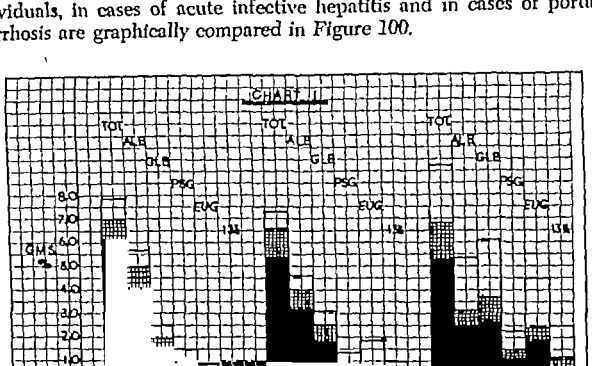

Fig. 100.—Serum protein fractions in liver disease. Total height of column shows maximum value in grams per 100 cc.; height of crosshatched column shows the average value; height of solid column gives the minimum value.

2. *Biliary Cirrhosis.*—The findings in a small group of patients with biliary cirrhosis of both primary and secondary types are given in Table 7. All these cases had gross enlargement of liver and spleen. The correctness of the diagnosis in the first case was established at autopsy. In only two of these cases, both of long standing, was the total globulin more than 3 gm. per 100 cc., and in only one was any of the abnormal "13½ per cent fraction" found.

Miscellaneous Hepatic Conditions.—Serum protein fractionation has been carried out on a number of patients suffering from various other hepatic conditions. The values are given in Table 8.

In the cases described as having secondary hepatic carcinoma there was, in every instance, considerable involvement of the liver which was grossly enlarged at the time of the examination. Both in these and in the cases of malignant and nonmalignant obstruction of the com-

TABLE 7

SERUM PROTEINS IN BILIARY CIRRHOSIS

Case No.	Serum van den Bergh (units)	Duration of Jaundice	Serum Proteins (gm./100 cc.)				Remarks
			Total	Albumin Fraction	Globulin Fraction	13½% Fraction	
1	40.0	3 years	6.2	3.7	2.5	0	Primary biliary cirrhosis.
2	15.6	7 months	6.9	4.3	2.6	0	Primary biliary cirrhosis.
3	1.8	Repeated bouts: 3 years	7.0	4.1	2.9	0	Secondary biliary cirrhosis from stenosis of common bile duct.
4	9.0	Repeated bouts: 6 years	7.0	3.8	3.2	0	Secondary biliary cirrhosis from stenosis gf common bile duct.
5	4.5	Repeated bouts: 24 years	6.0	2.5	3.4	0.8	Secondary biliary cirrhosis from stenosis of common bile duct.
5	....	Increasing jaundice	6.3	1.9	4.4	1.5	Two months later: just prior to death.

TABLE 8

SERUM PROTEINS IN MISCELLANEOUS HEPATIC CONDITIONS

Case No.	Serum Proteins (gm./100 cc.)				Remarks
	Total	Albumin Fraction	Globulin Fraction	13½% Fraction	
1	7.5	3.0	4.5	2.1	Primary carcinoma of liver (in a cirrhotic liver).
2	4.7	1.8	2.9	0	Secondary carcinoma of liver.
3	6.8	4.8	2.0	0	" " " "
4	4.8	2.5	2.3	0	" " " "
5	6.2	3.0	3.2	0.9	" " " "
6	6.2	3.7	2.5	0.5	" " " "
7	5.1	2.9	2.2	0	
8	6.8	3.6	3.2	0	Obstructive jaundice (stone).
9	7.4	4.9	2.5	0	" " "
10	5.9	3.4	2.5	0	" " "
11	4.4	2.9	1.5	0	Obstructive jaundice (carcinoma).
12	5.2	2.8	2.4	0	" " "
13	6.5	3.9	2.6	0	" " "
14	6.2	4.1	2.1	0	" " "
15	6.3	4.0	2.3	0	Hodgkin's disease involving the liver.

mon bile duct, the main abnormality found was a decrease in the serum albumin accompanied by only a mild increase in the serum globulin. In the case of primary carcinoma of the liver, a marked increase in the serum globulin is noted but it is felt that this is associ-

ated more with the cirrhotic process which was present than with the hepatoma.

COMMENT

The observations given above indicate that a characteristic disturbance occurs in the serum proteins of patients who have parenchymal disease of the liver. This disturbance is characterized by a rise in the serum globulins and by a more or less corresponding fall in the serum albumin. The rise in serum globulin is largely accounted for by an increase in the euglobulin fraction, the pseudoglobulins being only mildly elevated. It will be noted, too, that the elevation of the euglobulin fraction above normal levels is almost entirely due to the appearance of the abnormal "13½ per cent fraction" which amounts to 1 gm. or more per 100 cc. in most cases of cirrhosis. The presence of this "13½ per cent fraction" in any quantity is definitely abnormal and, as its qualitative detection is very simple, a test for its presence serves as a rapid means of recognizing a definite and significant serum protein abnormality.

This disturbance in the serum protein picture is much more marked in patients with diseases which affect primarily the parenchymal cells than it is in those in whom the hepatic symptoms are associated with other causes, such as invasion with secondary neoplasm or biliary tract obstruction. In acute hepatitis the disturbance is relatively mild and disappears with recovery from the liver infection. In cirrhosis of the liver of the Laennec type the abnormalities may be much more pronounced. In the later stages, however, where there is marked cachexia and often increased loss of protein by repeated paracenteses, not only is the serum albumin definitely lowered but the elevation of the serum globulin and the "13½ per cent fraction," so commonly found in less advanced cases, may be absent. Whether such patients did have a high serum globulin in an earlier stage of their disease we do not know. As a result of treatment we have seen an occasional patient show an increase in the serum albumin but in most there has not been any striking change in the relatively short time that they have been under our observation. We have not, as yet, sufficient data upon which to reach a final conclusion but the results that we do have would suggest that such an improvement in the serum albumin is more likely to take place in patients whose cirrhosis has been associated with alcoholism and defective nutrition than in those in which these have not been factors. We would agree that such an increase in serum albumin is of good prognostic significance, as it probably indicates an improvement in the protein-forming power of the liver and is also associated with improvement in the patient's general nutrition.

In the small number of cases of biliary cirrhosis that we have been able to investigate, gross abnormalities were detected in only one patient whose common duct had been damaged twenty-three years

previously and who, in spite of efforts to bring about surgical repair, had had repeated bouts of fever, pain and jaundice. She was known to have biliary cirrhosis for at least ten years prior to her death. In two cases of primary biliary cirrhosis the serum proteins showed only slight abnormality. This finding favored the diagnosis of biliary cirrhosis, which was confirmed in the one fatal case.

No striking change in serum globulins was found in patients suffering from the various forms of extrahepatic jaundice or from secondary carcinoma of the liver, but in the carcinomatous cases a decided fall in serum albumin level was a frequent finding.

Although the results of the Takata-Ara, cephalin-cholesterol flocculation and formol-gel tests in these cases are not given in the tables, our findings are in complete agreement with other work[6, 13] which has shown that the results of these tests are intimately associated with the globulin portion of the serum protein, and particularly with the euglobulin fraction.

Hypoalbuminemia, of course, is found in many of the clinical conditions, summarized by Loeb,[15] arising either from inadequate protein intake, excessive protein loss, or failure of albumin synthesis. The last of these is felt to be the cause in patients with hepatic disease as there is fairly good evidence that the liver plays an important part in the production of serum albumin. Hyperglobulinemia, too, is found in a number of diseases, particularly infections such as lymphogranuloma inguinale, Boeck's sarcoid, rheumatoid arthritis, kala-azar, subacute bacterial endocarditis, and many others. It is also associated with certain neoplastic conditions, particularly multiple myeloma where very high values are at times encountered. Many such cases show the abnormal "13½ per cent fraction" as well.

The findings, then, of hypoalbuminemia, hyperglobulinemia, and the presence of the "13½ per cent fraction" are not diagnostic of cirrhosis of the liver but, in those cases in which the history and physical findings direct one's attention to the liver, the occurrence of these changes in the serum proteins may assist one in arriving at such a diagnosis.

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ACUTE INFECTIONS OF THE LIVER

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THE prevalence of acute epidemic infective hepatitis among Service personnel in World War II has stimulated the study of this and allied diseases. Although handicapped by lack of a susceptible laboratory animal for experimental investigation, material additions have been made to knowledge of the etiology and pathology of this disease by means of transmission experiments in human volunteers and the use of aspiration biopsy. Clinical studies, too, have been conducted with emphasis directed toward the study of impairment of hepatic function by means of various laboratory tests. While such studies have helped to a better understanding of infections of the liver, it is important to remember that the diagnosis and treatment of these infections are not dependent upon elaborate laboratory tests but rather upon clinical observation.

This discussion will be confined to those infections in which impairment of function of the polygonal cells of the liver is a frequent or constant manifestation (acute diffuse hepatitis) and to a group of suppurative infections in which the liver is the chief site of the disease but in which disturbance of function of the hepatic parenchyma is not a major feature (acute suppurative hepatitis). These diseases may be classified as follows:

Acute Diffuse Hepatitis:

- Infective Hepatitis { epidemic / sporadic
- Homologous Serum Jaundice
- Yellow Fever
- Weil's Disease

Acute Suppurative Hepatitis:

- Amebic Hepatitis { with abscess / without abscess
- Abscess of Liver (nonamebic) { single / multiple
- Acute Suppurative Pylephlebitis

ACUTE DIFFUSE HEPATITIS

Epidemic Infective Hepatitis.—Transmission experiments in human volunteers indicate that this disease is caused by a filtrable organism

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which is present in the blood, stools and, perhaps, in the nasal washings of patients. Experimentally, the disease is transmitted by ingestion, inoculation and, less consistently, by nasal spray. Epidemiologic studies have suggested that the mode of spread and the portal of entry may vary in different epidemics. Convincing evidence of spread through the gastrointestinal route has been reported in some epidemics and in others there has been evidence suggesting transmission through the respiratory route. The incubation period would appear to be two to four weeks. It has been shown that one attack confers a high degree of immunity. The disease occurs most commonly in young people; it is rarely found in those over 40 years of age. There is no significant sex incidence. Epidemics have been common among soldiers for generations, and World War II was no exception. The disease was particularly prevalent in the Mediterranean theater where it occurred chiefly in summer and autumn, tending to fall off in November.

Distinctive lesions occur only in the liver. These are of two types: (1) degeneration of the cells of the hepatic parenchyma, most marked in the central vein area and ranging in severity from cloudy swelling to necrosis; (2) infiltration of the portal areas with lymphocytes and mononuclear cells. Such changes are manifest a week after the onset of icterus and usually subside within a month. It is worthy of note that the stroma and blood vessels of the liver are relatively unaffected. During recovery the regenerating cells grow in a regular manner and, thanks to the persistence of the supporting stroma, the normal architecture of the liver with its important relation of cells, ducts and blood vessels is maintained.

Clinical Manifestations.—The onset of jaundice is preceded in virtually all cases by a prodromal period of two to seven days, which is characterized by malaise, fatigue, lassitude and loss of appetite sometimes accompanied by nausea, vomiting and diarrhea. The most consistent and striking symptom in this preicteric stage is loss of appetite. While sometimes mild, it often goes on to complete anorexia and, less frequently, to nausea aggravated by the smell or sight of food. Vomiting is present in about one-third of the patients; in a few, this symptom persists and constitutes a therapeutic problem.

Although anorexia and malaise are the most constant manifestations of the prodromal period, a definite febrile stage, temperature 100° to 104° F., precedes or accompanies them—often confusing the diagnosis —in one-third of the cases. Then chilliness, occasionally a true rigor, and body aches dominate the picture until the gastrointestinal symptoms assume prominence and suggest the diagnosis. The fever usually lasts one to four days, rarely as long as ten or even twenty days; then, with the appearance of jaundice, the temperature falls sharply to normal. Less often, after a short febrile period the temperature returns to normal and the patient appears to have recovered; then, after a few days

or even two or three weeks, fever recurs for a day or two and jaundice develops.

Three distinct types of abdominal distress may be found. Mild abdominal pain, dull and aching in character, is commonly present; it is situated in the right upper quadrant and is always associated with enlargement and tenderness of the liver. Pylorospasm, giving rise to a more severe pain which sometimes is confused with biliary colic, occurs less frequently. Epigastric soreness may be a consequence of persistent vomiting. Slight to moderate enlargement of the liver, nearly always associated with tenderness, occurs in 80 per cent of the cases and usually precedes the appearance of jaundice by two or three days. The spleen is sufficiently enlarged to be felt on careful palpation in approximately 10 per cent of all cases.

Jaundice usually appears two to four days after the onset of malaise and anorexia, but may be delayed for a week or occasionally longer. It deepens gradually except in very severe cases when it may increase with marked rapidity. The urine becomes dark; this sign may provide the earliest indication of jaundice, particularly in male patients. In all but the mildest cases the stools become lighter in color; in the more severe cases they become clay-colored. With the onset of jaundice fever decreases in most cases, but may continue between 99° and 100° F. for ten to fourteen days. In rare instances, the high fever of the prelcteric stage may persist for some days. Nausea and vomiting, if present, usually diminish in severity; malaise and anorexia persist but become less pronounced. The jaundice lasts up to sixty days, and occasionally longer. In a series of 3000 cases observed in Canadian troops in the Mediterranean theater the average duration, from the first suggestion of jaundice to disappearance of bile from the urine, was sixteen days.

Just as anorexia is the most striking early symptom of onset, return of appetite is characteristically the first indicaton of recovery. An increase of pigment in the stool and a decrease of jaundice soon follow. The liver, enlarged in the acute phase, gradually becomes smaller and usually regains its normal size by the time jaundice has disappeared. Strength and energy return more gradually: it is usually four to eight weeks before the patient is fully recovered. Occasionally a recrudescence characterized by mild loss of appetite and slight liver enlargement without jaundice occurs within a week of the disappearance of bilirubinuria; in such cases a further period of rest usually leads to complete recovery. In 97.5 per cent of cases soldiers were returned to their units fit for combat duty, the average total duration of the illness being fifty days.

Variations in the usual course of the disease are noted occasionally. Enlargement of the liver, with or without jaundice, accompanied by loss of energy, mild malaise, impairment of appetite and dyspepsia, may persist for several weeks or even months. Even in such cases

eventual recovery is the rule and cirrhosis, if it ever results from this disease, must do so very rarely. Relapse with reappearance of all the symptoms and signs of the primary attack, usually in more severe form, may occur. Such relapse was observed in 2.5 per cent of the 3000 cases in the Mediterranean area. It usually occurred within four months of the primary attack; after this period relapses were less frequent and less severe; none occurred more than a year after the primary attack. It is notable that a history of previous jaundice was obtained from only ten of the 3000 patients.

Death from acute necrosis of the liver is a rare termination of this disease: there were two fatalities in our 3000 cases. The onset of drowsiness, persistent vomiting or delirium, and rapidly deepening jaundice are warning symptoms which may appear at any time during the course of the disease and may be followed by coma and death in a few days.

The natural history of the disease is that of an acute systemic infection, with evidence of selective damage to the parenchymal cells of the liver and exhibiting a strong tendency to recovery. In the mildest cases jaundice is very slight and transient; there is evidence that the infection can occur without jaundice.

Laboratory Findings.—Bile pigment is increased in the blood and may be measured quantitatively by the van den Bergh test or, less specifically, by the icterus index. The urine contains bile and excessive amounts of urobilinogen early in the course of the disease, usually two or three days prior to appearance of visible jaundice. If the stools become acholic, urobilinogen disappears from the urine and is not found again until hepatic excretion of bile is reestablished. Bile and often abnormal amounts of urobilinogen continue to be found in the urine until the jaundice has nearly disappeared. In the preicteric period the white blood count tends to be low with a relative lymphocytosis. Leukocytosis is not found except in rare cases of acute necrosis. A mild anemia with a normal color index occurs only in cases of prolonged jaundice. A change in the globulin fraction of serum proteins occurs in nearly all cases and reactions dependent upon this abnormality, such as the cephalin-cholesterol flocculation and thymol turbidity tests, are positive. Dye excretion tests, such as the bromsulfalein test, are of course impaired but need not, and should not, be used in the presence of jaundice.

The carbohydrate function of the liver, as shown by the glucose tolerance and galactose tolerance tests, is impaired in severe cases. In these the oral glucose tolerance test gives a characteristic result. The fasting blood sugar is low normal or lower; the peak, occurring usually at the second hour, is high, ranging up to 250 mg. At the height of the jaundice the fall is delayed but the blood sugar eventually drops to levels of 60 to 40 mg. at about the fifth hour. When tests are done as jaundice is clearing, a high peak is still found but the fall to hypo-

glycemic levels is more rapid. Glucose tolerance tests are of but little practical value in the investigation of jaundice and may indeed lead to an erroneous diagnosis of diabetes mellitus. The galactose tolerance test, on the other hand, may be helpful in the differentiation of jaundice due to acute diffuse hepatitis and that caused by obstruction of the large ducts. Characteristically the patient with acute hepatitis in the stage of deep jaundice will excrete at least two and commonly three or more grams of galactose in the urine in five hours following the ingestion of 40 gm. whereas in uncomplicated obstructive jaundice, as in the normal individual, it is rare to find more than 2 gm.

Serum alkaline phosphatase tends to be slightly or moderately increased; rarely is it over 25 Kay-Jenner units (normal, 5 to 10 units). While impairment of galactose tolerance in conjunction with a normal or only slightly increased serum phosphatase is strongly indicative of severe parenchymatous disease, such tests are rarely necessary to establish the diagnosis of epidemic infective hepatitis.

The diagnosis usually is easy. The development of jaundice preceded by a prodromal period of illness, with or without fever but with loss of appetite as a prominent symptom, is evidence of intrahepatic jaundice. The course of the disease and the existence of an epidemic of infective hepatitis confirm the diagnosis. In the prelcteric period, diagnosis is uncertain; the disease may be suspected, however, during an epidemic in patients with acute illness without localizing symptoms when loss of appetite is pronounced and leukopenia is present.

Treatment.—Rest until jaundice has cleared, appetite and sense of well-being have returned and the liver enlargement has subsided is the most important single factor in treatment. Animal experiments have shown that the liver is protected from hepatic poisons by ingestion of diets rich in carbohydrate and protein. Although there is no clinical evidence to indicate that the course of infective hepatitis is modified by diet, it is reasonable and wise to provide an appetizing diet high in carbohydrate and protein and moderate in fat. Above all, however, the patient must be encouraged to eat and foods which appeal should be given freely. If the patient is able to take adequate quantities of whole milk or skimmed milk, or drinks prepared from powdered skimmed milk, the supply of essential amino acids, such as methionine and cystine, is provided. When necessary, such foods may be given by duodenal tube. Intravenous amino acid preparations rarely are indicated but they may be used to augment feeding in the few severe cases when nausea and vomiting persist and prevent adequate oral feeding. Fluid intake should be sufficient to prevent dehydration; if vomiting is severe, the intravenous administration of glucose in saline may be required. The bowels should be kept open by means of mild saline laxatives.

No specific treatment for this disease is known. Vitamin supplements, methionine, cystine, choline, liver extract, insulin and glucose

have all been used but, as yet, there is no clinical evidence that any of them affect the natural course of the disease.

Sporadic Infective Hepatitis.—This form of liver disease, occurring mostly in young people but occasionally in older people, is indistinguishable clinically from the epidemic form in the individual case. The etiology is unknown. However, the similarity of the clinical manifestations of this disease and epidemic infective hepatitis, together with the fact that pathologically they are indistinguishable, suggest that they are similar, if not identical, diseases.

The onset may be febrile. Gastrointestinal symptoms—notably, loss of appetite—characterize the prodromal period in the majority of cases. The subsequent course of the disease is similar to that of the epidemic form except that relapse appears to be less common.

Worthy of special consideration is sporadic infective hepatitis occurring in patients over 40 years of age. Because this disease occurs more frequently in younger people, whereas jaundice due to obstruction of the common bile duct by stone or neoplasm is more common in the older group, diagnosis is sometimes in question. When the onset is typical with marked anorexia in the preicteric period, there is little difficulty. Jaundice due to obstruction of the common bile duct by stone is virtually always preceded by one or more attacks of biliary colic which differs in character, site, severity and duration from the upper abdominal distress of diffuse hepatitis. Obstruction of the common duct by tumor is usually painless but jaundice may be preceded by a variable period of persistent pain rather poorly localized across the epigastrium and not uncommonly radiating to the back. Hepatic enlargement is a frequent finding in jaundice due to diffuse hepatitis. It is not a feature of uncomplicated common duct obstruction but may be found in obstruction due to stone if there be cholangitis and secondary hepatitis with or without multiple abscesses. Obstruction from carcinoma is associated with enlargement of the liver only if there are widespread metastases in the liver. Splenomegaly is strongly indicative of primary intrahepatic disease but may occur in the rare cases of biliary cirrhosis secondary to prolonged or recurrent obstruction of the common duct by stone.

The greatest difficulty in diagnosis is encountered in those patients where the onset is insidious and not marked by a clear-cut loss of appetite, where hepatomegaly is not prominent, splenomegaly is absent, jaundice is deep and persistent, the stools are acholic and the urine contains bile but no urobilinogen. In such a case, carcinoma of the head of the pancreas or silent stone in the common bile duct as the cause of jaundice must be considered in the differential diagnosis. Liver function tests, particularly the galactose tolerance test and the serum alkaline phosphatase test, may be of considerable help. In any where doubt exists, laparotomy should be delayed. Silent stone

as a cause of persistent jaundice is very rare, and operative treatment of carcinoma of the head of the pancreas is, at best, palliative.

Homologous Serum Jaundice.—This term has been applied to hepatitis caused by a filter-passing agent transmitted in human blood and blood products. Hepatitis has been observed after the administration of measles and mumps convalescent serum, yellow fever and pappataci fever vaccines containing human serum, liquid and reconstituted dried serum or plasma and, also, after whole blood transfusions.

Infection has resulted from inoculation with as little as 0.01 cc. of the material containing the icterogenic agent, and the disease has followed administration by inoculation, ingestion or intranasal spray. The incubation period is forty to 160 days—usually eighty to 120 days—as compared to fourteen to thirty-five days in infective hepatitis. The agent has been demonstrated in the blood of patients suffering from the disease but not in their stools.

The *pathology* of this form of hepatitis is indistinguishable from that of infective hepatitis. The clinical course, too, is similar in the individual case. However, the mortality is somewhat variable and may be quite high in wounded soldiers; death is due to acute necrosis of the liver.

The exact nature and the origin of the causative agent are not known. The early view that this disease was due to the same agent as epidemic infective hepatitis which was transmitted by inoculation of blood or blood products cannot be accepted as established. The different incubation periods and the failure to demonstrate cross-immunity between the two diseases make it unlikely that they are due to the same causative agent. It is possible that cases of sporadic infective hepatitis are caused by two different micro-organisms, one of which provides the reservoir for most epidemics of infective hepatitis, and the other that of homologous serum jaundice and possibly some epidemics of infective hepatitis.

The *treatment* of this disease is similar to that of other forms of acute hepatitis. Attempts have already been made to lessen its incidence by preparing vaccines free of human serum and by care in the selection of donors for transfusion. It is usually recommended that no donor be used who, in the previous year, has had jaundice, exposure to infective hepatitis or transfusion of blood or blood products. How successful such measures will be remains to be seen.

Yellow Fever.—As yellow fever does not occur in this locality, it will not be discussed in any detail. It is another virus disease, transmitted by the mosquito Aedes aëgypti, in which damage to the hepatic cells is a prominent feature. Although severe systemic manifestations tend to mask the early symptoms of acute liver disease yet, as in other forms of acute diffuse hepatitis, jaundice is preceded by [illegible]

dromal period of a few days in which loss of appetite and sometimes nausea and vomiting are pronounced.

Weil's Disease.—Weil's disease is a specific, febrile infection caused by Leptospira icterohaemorrhagiae. It is characterized by manifestations of an acute systemic infection with evidence of damage to liver and kidneys in most, and to other organs in many cases.

The spirochete has been found in the rat, mouse, dog, cat, pig, fox, mongoose, horse, mink, bat, bandicoot and poultry. In all human epidemics and in most sporadic cases the common gray rat has been the source of the infection; approximately 10 per cent of these rodents are infected. While it is possible for infection to occur through contamination of cuts and abrasions or from the bite of a rat, in most instances human infection has been attributed to ingestion of water or food contaminated by urine or feces of infected rats. For this reason, Weil's disease is an occupational hazard to those who work in wet, rat-infested places. Epidemics have been reported among bargemen, wharf workers, fishmongers, sewer workers, poultry dressers, miners, slaughterhouse workers, garbage men and soldiers in trenches. It has been acquired by bathing in contaminated water, particularly in stagnant canal water.

Pathology.—Following infection by any route, the spirochetes are disseminated by the blood stream and invade various organs of the body. They soon disappear from all organs except the liver, heart muscle and kidneys, in which tissues pathological changes are most striking. Damage to the liver varies from the mildest evidence of degeneration in the polygonal cells to necrosis, with periportal infiltration of polymorphonuclear leukocytes and lymphocytes. The cells of the renal tubules show a variable degree of swelling and degeneration with necrosis in severe cases. The glomeruli are swollen and filled with exudate and precipitated bile pigments. The capsular endothelium is proliferated and, in protracted cases, fibrosis may be marked. Hemorrhage into glomeruli may be sufficient to simulate acute glomerulonephritis. Cardiac damage, too, is variable: gross hemorrhage is often found under the pericardium and the endocardium; on microscopic examination, subendothelial hemorrhage and round cell infiltration of myocardium may be noted and, in severe cases, vacuolar and granular degeneration of muscle fibers is found. Hypertrophy and engorgement of spleen and lymph nodes and petechial and purpuric hemorrhages in the skin, mucous membranes, conjunctivae and retinae may be found, as well as hemorrhage, cellular exudate and degenerative changes in striated muscles.

Clinical Manifestations.—Following an incubation period of five to twenty days, the disease progresses through three stages, somewhat ill-defined and shading one into the other. The *septicemic stage* marks the onset, lasting three to seven days; it is characterized by chills, fever, malaise, prostration, headache and pain in the limbs and back.

The temperature may reach 105° F. The conjunctivae frequently are injected and ocular movements are painful. Petechial and purpuric hemorrhages in skin and mucous membranes often occur, and epistaxis is common. Pain in the limbs is usually accompanied by localized areas of tenderness, particularly in the legs and back, and is associated with a definite lesion in the muscles. Headache may be severe with coexisting signs of meningeal irritation and increase in the pressure, cells and proteins of the cerebral spinal fluid. The urine frequently contains albumin but usually in amounts often found in any severe, acute infection. Definite evidence of liver damage is lacking at this time although profound loss of appetite or persistent nausea and vomiting usually presage the development of jaundice. In epidemics, some cases never progress beyond this septicemic stage but may be recognized as Weil's disease by means of laboratory studies, stimulated by the knowledge of the patient's occupation or the existence of an epidemic.

The septicemic stage blends gradually with the second or *hepatorenal stage* in which evidence of damage to various organs—in particular, the liver and kidneys—becomes apparent. Jaundice appears and deepens rapidly. The liver becomes enlarged and tender, the urine contains bile and excessive amounts of urobilinogen, and the stools become light in color. In the most severe cases, the stools become acholic and urobilinogen disappears from the urine. The spleen is palpable in about 10 per cent of cases. Nausea and vomiting tend to subside but usually the patient appears toxic and lethargic and the fever continues. During this stage the albuminuria increases and oliguria develops with red blood cells, white blood cells and granular casts appearing in all but the mildest infections. In the more severe cases, oliguria is pronounced; in some, anuria develops and, in fatal cases, is an almost constant finding. There is retention of metabolites in proportion to the renal damage and the blood pressure rises.

The *convalescent or recovery stage* begins in the third to sixth week of the disease. Fever subsides, urinary output increases and abnormal constituents in the urine decrease. Jaundice usually is the last sign to disappear; it may persist for several weeks. About 20 per cent of the cases relapse between the third and fifth week. The mortality rate is usually about 30 per cent in patients developing hepatic and renal damage but varies considerably in different epidemics. In the others recovery is usually complete.

Laboratory studies reveal an almost constant leukocytosis with increase in polymorphonuclear leukocytes. The hemorrhagic manifestations usually appear first in the septicemic stage before evidence of liver damage is marked, and are not usually associated with prolongation of the prothrombin time or deficiency in platelets but rather with toxic damage to the capillary endothelium. Prothrombin deficiency may occur later: rarely because of prolonged exclusion of bile

whom such a state exists. If this state of equilibrium is disturbed and the balance swings in favor of the parasite, the patient may become ill showing evidence of (1) disturbance in function of the large bowel with symptoms varying in degree from those characteristic of the so-called irritable colon to those of dysentery, the latter a rather uncommon manifestation of amebic infection; (2) symptoms resulting from invasion of distant organs, notably the liver. Such invasion of the liver may complicate the course of amebic infection of the bowel at any time and, as shown in Table 1, may be associated with any degree of severity of the bowel lesion. The cases recorded here were observed in Canadian soldiers serving in Italy and in veterans who had served in an area where amebiasis was endemic but whose infection was not recognized prior to return to Canada.

The parasites reach the liver by way of the portal blood stream and lodge usually in its right lobe, probably because the portal blood from the colon passes almost entirely to this lobe. Here the parasites reproduce by binary fission but do not encyst. Liquefactive necrosis produces a cavity or cavities which tend to coalesce and form, usually, a single abscess. The abscess is filled with liquefied tissue, blood and bile having the appearance of "anchovy sauce." The parasites are demonstrated with difficulty in the amebic pus but more easily in the wall of the abscess. Damage to the liver is local and not diffuse.

The early *symptoms* of amebic abscess are those of severe, acute infection: malaise, fatigue, fever, chills, sweating and leukocytosis, with localizing signs and symptoms dependent on the site of the abscess. Symptoms from involvement of adjacent structures appear later. Hepatic enlargement, associated with tenderness, is almost constant. Dull pain in the liver area, apparently due to stretching of the capsule, is frequent but may not appear until days or weeks after the onset of the early symptoms. When the abscess is near the surface, perihepatitis with resultant irritation of the parietal peritoneum gives rise to pain aggravated by movement or breathing. As amebic abscess usually is situated near the superior surface of the liver, diaphragmatic irritation may give rise to pain in the lower chest and shoulder tip, simulating pleurisy. In association with this are found fixation of the diaphragm in the expiratory position and sometimes either a sterile pleural effusion or partial lower lobe atelectasis simulating pneumonia.

Complications of amebic abscess may result from spread of the infection by direct extension or through the blood stream and from secondary infection of the abscess by bacteria. The abscess may rupture into the peritoneal cavity and give rise to general peritonitis or, more commonly, into the subdiaphragmatic area, producing subphrenic abscess. Rupture into the pleural cavity may occur, producing empyema, or into the right lung with consequent lung abscess. Spread of the infection by invasion of the hepatic veins may result in hematogenous amebic lung abscess in either lung.

The *diagnosis* of amebic liver abscess depends upon recognizing the liver as the site of a severe localized infection. It should be suspected in any patient with symptoms and signs of such infection, who has been exposed at any time to amoebic infection. A history of chronic diarrhoea, past or present, is suggestive but not essential to the diagnosis. Similarly, the demonstration of endamoeba histolytica in the stools is strong supporting evidence but liver abscess due to amoebiasis can occur after the bowel lesion has healed entirely.

The *treatment* of uncomplicated liver abscess consists in general supportive measures, symptomatic treatment and the intramuscular administration of emetine hydrochloride, 0.032 to 0.065 gm. (½ to 1 grain) daily until a total of 0.45 to 0.65 gm. (7 to 10 grains) have been given. In most cases such treatment is all that is necessary but sometimes aspiration of the abscess, when its location can be determined, is also required. Surgical drainage should be avoided if possible and never attempted until the other methods have been tried. When secondary infection has occurred, the use of other chemotherapeutic agents or antibiotics aid in control of the infection but repeated aspiration or surgical drainage is necessary to complete cure.

Amebic Hepatitis without Suppuration is a poorly understood condition manifest by hepatic enlargement with tenderness, fever and leukocytosis of variable degree, and sometimes peritoneal irritation similar to that of liver abscess occurring in patients who have or have had colonic amebiasis. The pathology of the condition is not known but it is thought to represent an early stage in the development of liver abscess. Treatment with emetine hydrochloride, as for liver abscess, yields excellent results. The knowledge that emetine hydrochloride, while highly efficacious in controlling the systemic manifestations of amebiasis and in destroying the parasites in the liver, is not as effective as other amebicidal drugs in eliminating the infection from the colon renders necessary the administration of diodoquin or some similar preparation following emetine therapy.

Acute Abscess of the Liver may arise from infection elsewhere in the body, usually in the gastrointestinal tract. The infection may reach the liver by way of either the systemic or portal circulation. Table 2 presents the findings in twenty-three cases treated at the Toronto General Hospital between 1926 and 1946. Pylephlebitic abscesses are not included. It is apparent that the most commonly demonstrated source of infection was the biliary tract. The diagnosis should be made when symptoms of abscess, chills, fever, sweating and malaise are combined with symptoms and signs localizing the disease to the liver. Enlargement and tenderness of the liver are almost constant. Pain in the liver area and pain from irritation of the parietal peritoneum, including that of the diaphragm, occur less frequently. This disease carries a high mortality even with the use of chemotherapy and antibiotics as adjuncts to surgical drainage.

TABLE 2

LIVER ABSCESS: FINDINGS IN TWENTY-THREE CASES TREATED IN THE TORONTO GENERAL HOSPITAL, 1926 TO 1946 INCLUSIVE

Case	Age	Sex	Source of Infection	Organism	Duration (weeks)	Site (lobe)	Number of Abscesses	Jaundice	Treatment		Result	Autopsy
									Chemotherapy	Operation		
1	45	M	Gallbladder	Str. anaerobius	7	Right	Single	−	−	−	Died	Yes
2	67	M	Gallbladder (cholangitis; stone in common duct)	B. coli; Streptococcus	5	Right and left	Multiple	+	−	−	Died	Yes
3	62	M	Gallbladder	Str. anaerobius	20	Right and left	Multiple	−	Sulfonamides	Surgical drainage	Died	Yes
4	55	F	Gallbladder (cholangitis; stone in common duct)	Staph. aureus; Gram-neg. bac.	15	Right and left	Multiple	+	−	Cholecystectomy	Died	Yes
5	71	F	Gallbladder (cholangitis; stone in common duct)	B. coli	3	Right and left	Multiple	+	−	−	Died	Yes
6	51	M	Gallbladder (gangrene)	B. coli; Str. hemolyticus	3	Left	Single	−	−	Surgical drainage	Died	Yes
7	..	F	Pelvis (actinomycosis)	Actinomyces	100	Left	Single	−	−	Surgical drainage	Recovered	...
8	57	M	Lung (actinomycosis)	Actinomyces	40	Right and left	Multiple	−	−	−	Died	Yes
9	49	M	Lung (actinomycosis)	Actinomyces	64	Right	Single	−	−	Surgical drainage	Died	Yes
10	36	M	Skin (furunculosis, 4 months before)	Staph. aureus	8	Right	Single	−	Sulfonamides	Surgical drainage	Recovered	...
11	29	F	Appendix	Str. anhemolyticus	6	Right	Multiple	−	Sulfonamides	Surgical drainage	Died	No
12	70	M	Liver (primary carcinoma)	Str. hemolyticus	6	Right	Single	−	−	Surgical drainage	Died	Yes
13	42	M	Duodenum (ulcer with abscess)	?	1	Left	Single	−	−	−	Died	Yes
14	40	F	No data									
15	40	M	Duodenum (ulcer with abscess)	Staph. aureus	6	Left	Single	−	−	−	Died	No
16	50	F	Unknown	?	1	Right and left	Multiple	−	−	−	Died	Yes
17	47	F	Unknown	Staph. aureus	5	Right and left	Multiple	−	−	−	Died	Yes
18	68	F	Unknown	Str. anaerobius	6	Right	Single	−	Sulfonamides	−	Died	Yes
19	31	M	Unknown	Str. anaerobius	2	Right and left	Multiple	−	−	Surgical drainage	Died	Yes
20	43	M	Unknown	Str. anhemolyticus	6	Right	Multiple	−	−	Surgical drainage	Died	Yes
21	43	M	Unknown	Str. anaerobius	4	Right	Single	−	Sulfonamides	Surgical drainage	Died	Yes
22	74	F	Unknown	B. coli; Staph. aureus	2	Right	Single	−	Sulfonamide and penicillin	Surgical drainage	Recovered	...
23	34	M	Unknown	No data							Died	Yes

TABLE 3

PYLEPHLEBITIS: FINDINGS IN FOURTEEN CASES TREATED IN THE TORONTO GENERAL HOSPITAL, 1926 TO 1946, INCLUSIVE

Case	Age	Sex	Source of Infection	Organism	Spread	Duration (weeks)	Jaundice	Ascites
1	34	M	Appendix	Str. hemolyticus; B. coli	Lungs	1	–	–
2	55	M	Appendix	B. coli	–	3	–	–
3	19	M	Appendix	Str. anhemolyticus	Meninges	7	+	+
4	23	M	Appendix	B. coli; Str anhemolyticus	–	5	–	+
5	24	M	Appendix	B coli; Str. hemolyticus; Str. anhemolyticus	–	6	–	–
6	32	M	Appendix	B. coli (mixed)	Lungs	8	–	–
7	43	F	Appendix	B. coli (mixed)	–	12	+ (stone in common bile duct)	–
8	48	M	Colon (diverticulitis)	B. coli	–	8	–	–
9	65	M	Colon (diverticulitis)	B. coli; Str. anhemolyticus; Staph. aureus	Lungs	8	–	–
10	69	M	Biliary tract (cholangitis)	B. coli	Lungs	4		
11	87	F	Biliary tract (cholangitis)	B. coli	–	1	–	–
12	58	M	Colon (acute ulcerative colitis)	B. coli	General septicemia	6	–	–
13	44	F	Meckel's diverticulum (peptic ulcer)	Str. hemolyticus; Str. anhemolyticus; Staph. aureus	–	2	–	–
14	26	F	Not known	Str. anhemolyticus	–	6	–	–

Acute Suppurative Pylephlebitis is a rare complication of infections occurring anywhere in the area drained by the portal vein and its tributaries. The findings in fourteen cases seen at the Toronto General Hospital from 1926 to 1946 are recorded in Table 3. The diagnosis was made during life in ten of these cases. Postmortem examination, carried out in all but one case, confirmed the diagnosis in nine and established it in the other four cases. The common source was an inflamed appendix.

The disease is manifest by swinging fever with chills, leukocytosis and progressive ill health characteristic of severe suppurative infections. Localizing symptoms and signs are scant. Hepatic enlargement is slight or absent and tenderness of the liver is not common. Jaundice is rare: it occurred in only two of the fourteen cases observed and in one of these was due to coincidental obstruction of the common bile duct by stone. The diagnosis is dependent upon recognition of a source in the portal area for a severe, suppurative infection in which localizing signs and symptoms are absent or, if present, suggest the liver as the site of the infection. The disease was fatal in all fourteen cases. No treatment effective in altering the progressively downhill course ending in death, usually within two months of the onset of the disease, was known prior to the discovery of penicillin and streptomycin. It is possible that these antibiotics may prove of value in the treatment of some cases.

COMMENT

Acute diffuse hepatitis, occurring with much greater frequency than the suppurative form, is not a single entity but a group of different diseases in all of which diffuse damage to the parenchymal cells of the liver occurs. This pathological process gives rise to disturbance in function and resultant symptoms and signs which are common to the group. On the other hand, these diseases differ one from another in the systemic manifestations of the infection and in damage to other organs when such occurs. No specific treatment is known for infective hepatitis or homologous serum jaundice but, fortunately, their mortality is low. Preventive measures may be effective in reducing the incidence of homologous serum jaundice but, as yet, there is insufficient knowledge of the mode of spread of sporadic and epidemic hepatitis to permit effective prophylaxis. The control of mosquitoes and the use of vaccine have decreased the incidence of yellow fever but no specific treatment for this serious infection is known. The prevention of Weil's disease has been discussed and the possibility of effective treatment in the early stages with penicillin mentioned.

Of the acute suppurative infections of the liver, pylephlebitis and nonamebic abscess fortunately are rare. The use of penicillin and streptomycin may reduce their mortality but evidence of this has not yet been established. Amebic infection of the liver is uncommon in

this part of the world but common elsewhere. Wider travel increases the possibility of its occurrence in areas where it is not endemic, this is already apparent from experience gained from observation of returned Service men and women. Its early recognition is important because of the excellent results of specific treatment in the pre-abscess stage.

DISEASES OF THE BILIARY TRACT

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THE extrahepatic biliary tract comprises the collecting systems of ducts leading from the porta hepatis to the ampulla of Vater. Extending as an offshoot from the main trunk are the cystic duct and gallbladder whose function is to protect against sudden changes in pressure, to act as a storage depot for bile and to concentrate the bile during periods of digestive inactivity. The gallbladder is a muscular organ with a concentration of fibers almost amounting to a sphincter at the entrance to the cystic duct. The common bile duct is sparsely supplied with muscle cells but its lower end has a concentration of muscle cells forming the sphincter of Oddi. In biliary disease pain may occur from strong contraction of either of these sphincters, usually on a stone, perhaps occasionally as a result of a primary autonomic disturbance.

The liver excretes bile continuously at the rate of about 1 liter per day; between periods of digestive activity the sphincter of Oddi is closed and the bile is diverted into the gallbladder where it is normally concentrated as much as fifteen times by absorption of water, and altered by a change in its acidity and by addition of mucus. On passage of food into the duodenum the sphincter of Oddi relaxes and the gallbladder empties, there being an especially vigorous response if the meal is fatty. A grossly diseased gallbladder fails to concentrate the bile materially and to empty promptly.

Bile is necessary for the intestinal digestion and absorption of various food constituents and of fats in particular. On its prolonged exclusion from the intestine, deficiency of vitamins D and K is likely to occur. A small amount of bile will, however, perform most of its functions and there is no absolute need for the concentration of bile that occurs in the healthy gallbladder. After cholecystectomy the bile passes down a dilated common duct in a continuous flow and there is no resultant gross impairment of function.

The great majority of the disorders of the biliary tract have to do with the presence of gallstones and their complications. The resulting symptoms are largely due to muscle spasm, obstruction of the cystic

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or common bile duct often with secondary infection, and reflex disturbances of other organs. In this discussion the etiology, incidence, clinical manifestations and complications of gallstones will be discussed in some detail; brief mention will be made of malignant disease involving the tract and of compression of the ducts by extrabiliary lesions.

GALLSTONES: INCIDENCE AND ETIOLOGY

Gallstones are very common. Although rare in childhood they have been found even at birth. The incidence increases slowly in adolescence and early adult life, rapidly in middle life, and is found to be high in old age. Blumberg and Zisserman actually report an incidence of 70 per cent in subjects over 70 years of age, a figure higher than is recorded in other series in which the range is usually from about 20 per cent upwards. Gallstones are more common in women than in men; pregnancy seems to be a contributory factor.

Infection used to be thought the most common cause of the formation of gallstones, but this idea had to be abandoned for lack of proof. Stasis in the gallbladder is probably not a significant factor. There appears to be an important relationship between the concentrations of the bile acids and the cholesterol in the gallbladder bile. Experimentally, Andrews has shown that when the ratio of bile acid to cholesterol falls from the normal range of between 1:20 and 1:30 to levels of 1:13 or lower, cholesterol is precipitated out. Other factors, namely the fatty acid concentration, the pH, the protein, the calcium content of the bile, also determine the precipitation of cholesterol, calcium bilirubinate, and other sediment. Whether these findings are applicable to human beings is not known.

One is little concerned about the presence in the gallbladder of stones that are not or have not been producing symptoms. In the majority of instances those found at autopsy appear to have caused no trouble. It is not uncommon to discover unsuspected stones in the gallbladder when making a survey of the gastrointestinal tract. One must, of course, make sure that in the absence of biliary colic they are not producing milder reflex symptoms.

GALLBLADDER STONE—BILIARY COLIC

The distinctive symptom of stone in the gallbladder is biliary colic. It varies in severity, location and duration and may simulate many diseases affecting both the chest and the abdomen. Usually by the time the patient sees the doctor there is a history of previous similar attacks to help one make a diagnosis. In the uncomplicated attack the distress starts as a bloated feeling, and increases to the point of steady pain, which may be situated either in the epigastrium or right hypochondrium, or both. If the pain persists for some time it tends to localize in the region of the gallbladder. The pain becomes intense

and may last for many hours. Occasionally there are superimposed long waves of increased pain which is seldom spasmodic like the pain in intestinal colic in which spasms of pain lasting from 5 to 60 seconds recur again and again. The pain of biliary colic is commonly referred to the inferior angle of the right scapula or to the interscapular region. It may be referred to the precordium, to the left hypochondrium, the right loin, or the upper lumbar region, and rarely it is localized to the left hypochondrium. We have observed a patient in whom the pain was referred to the right lower quadrant, and accompanied by urinary frequency. A number of patients have described their distress as a sensation of something bursting inside them. Vomiting commonly accompanies the pain, and sometimes gives relief; patients may try to induce it by tickling the back of the throat. In our experience vomiting is found in this condition just as commonly as in colic from common duct stone. Occasionally a patient feels chilly and may shake. That this is not a true rigor is indicated by the fact that there is no rise in temperature or leukocytosis, and that all symptoms clear quickly with the subsidence of the pain. It is possible that these "chills" are of nervous origin. The constitutional disturbance is apt to leave the patient exhausted for a day or two after the attack.

Mild transient jaundice may occur and helps to confirm the diagnosis. It usually escapes the notice of the patient and may be subicteric. It is readily demonstrated by measurement of the serum bilirubin which reaches levels of 1 to 2 mg. per 100 cc. During, or shortly after the attack the urine may become darker because of the presence of bile or urobilin. The stools may also be pale but this is usually due to a relatively increased intake of milk rather than to a decreased pigment content. In some cases there may be a reduction of the flow of pancreatic secretion producing a fatty stool.

Physical examination of the abdomen is an important diagnostic procedure during the attack, and for a day or two afterwards. Tenderness over the gallbladder area may be elicited by direct palpation or by careful jarring of the right cartilaginous plate, and occasionally one can feel the tender gallbladder. The liver is normal in size. Hyperesthesia in the region of the right scapular angle may be demonstrable during an attack in patients whose pain is referred to that area. Rigidity of the upper right rectus muscle is commonly found; one must remember, however, that spasm and tenderness of the upper rectus may occur as a result of vomiting or of lesions in the back or chest in the absence of any acute gallbladder disturbance. The physical signs associated with severe gallstone colic are similar to those of early superimposed acute cholecystitis.

Radiological investigation may be helpful but the findings are difficult to interpret and often misleading. Of course, one does not subject the patient to cholecystography during the attack of pain or in the presence of jaundice. The most informative finding is the demonstra-

tion of stones either as calcareous densities or as negative shadows in the cholecystogram. In only about a third of cases, however, are stones demonstrable. The most constant finding is a failure of the gallbladder to fill with the dye; the presence of a faint shadow or delayed emptying is also significant. A gallbladder that casts no shadow, that fills poorly, or empties slowly may, however, be quite normal. Such findings often depend on variations in absorption of the dye from the intestine as well as on its excretion by the liver rather than on factors inherent in the gallbladder. Not infrequently an apparently malfunctioning gallbladder will give a normal response if the test is repeated after biliary drainage. In some cases after the gallbladder has emptied, the dye may be reabsorbed from the gut and reappear in the gallbladder leading to persistence of the shadow. A large slowly emptying gallbladder may be found in patients who have an indolent gastrointestinal musculature, and, on the other hand, increased tone of the duodenum or sphincter of Oddi may also delay the emptying. Failure to demonstrate a normal shadow may also be due to technical difficulties related to obesity; and small gas bubbles overlying the gallbladder shadow may be confused with stones. For these reasons it is often wise to repeat the test. Repeated failure to demonstrate a shadow is usually evidence of obstruction of the cystic duct, less commonly of inability of the gallbladder to concentrate the dye.

In puzzling cases *biliary drainage* may be helpful. Microscopic examination of the three types of bile which are obtained may reveal crystals of cholesterol and calcium bilirubinate if stone is present. An inflammatory exudate which is associated with these crystals or which is deeply stained with bile may be assumed to have come from the biliary tract; otherwise the possibility that it has come from the upper respiratory passage, the stomach, the duodenum or the pancreas must be considered.

Patients subject to biliary colic sometimes give a history of a marked indiscretion in diet, not necessarily high in fat, just preceding the onset of pain; attacks may also follow jarring, such as a rough automobile ride, or intense emotional strain. In most instances, however, they come unpredictably at irregular intervals.

Treatment.—Milder attacks of biliary colic are often relieved by inhalation of amyl nitrite or ingestion of 0.6 mg. of nitroglycerin, repeated if necessary. If either of these does not suffice, demerol 50 to 100 mg. or opiates in appropriate dosage should be given and repeated if needed. Although there is experimental evidence that opiates increase pressure in the duct by causing spasm of the sphincter, yet they relieve severe pain better than any other drugs and are always indicated in violent attacks.

Since medical and dietary measures seldom prevent recurrence of the attacks, surgical procedures are often necessary, as indicated by the severity and frequency of the attacks, the occurrence of compli-

cations, the age and condition of the patient. If attacks are allowed to recur, serious complications are likely to develop which render operation more difficult and dangerous. Furthermore, secondary functional disorders of the gastrointestinal tract tend to become so firmly established that they will persist even after adequate surgical treatment. The occurrence of two severe attacks within a few years probably warrants a cholecystectomy. Older people withstand the operation well in the absence of severe related complications or serious disease in other systems.

Stone in the gallbladder may give rise to the following manifestations and complications which will be considered in order:

Acute Cholecystitis which may be complicated by:
- (*a*) Empyema of the gallbladder.
- (*b*) Gangrene of the gallbladder secondary to impaction of a stone in the cystic duct.
- (*c*) Perforation of the gallbladder.
- (*d*) Formation of a fistula between the gallbladder and some part of the gastrointestinal tract.

Hydrops of the Gallbladder.

Chronic Cholecystitis.

Common Duct Stone, which may be associated with:
- Attacks of colic.
- Obstructive jaundice.
- Cholangitis—acute.
  —chronic.
  —suppurative.
- Stricture.

ACUTE CHOLECYSTITIS

This condition is almost always secondary to temporary obstruction of the cystic duct and there is commonly a history of former attacks of biliary colic. If infection is present it is usually a secondary development which occurs in the later stage of a prolonged attack, the primary condition being the reaction of the lymph and blood vascular systems of the gallbladder to the obstruction. Early in the disease it is difficult to tell whether the patient is suffering from severe biliary colic or from cholecystitis, and there is no sharp dividing line between the two conditions. Infective cholecystitis such as occurs rarely in typhoid fever or other septicemias presents a different clinical picture.

Acute cholecystitis may occur at any age but is much more common in later decades. It is said to be rare in Negroes and hardly ever to occur in the Negro male. It is more common in women than in men. Patients tend to have multiple attacks which usually subside spontaneously.

Patients present themselves because of pain. Initially this is of the same nature, location and radiation as that of uncomplicated biliary colic; gradually it tends to change to an intense soreness over the

gallbladder with great local tenderness. Deep breathing aggravates the pain, as does anything that increases the pressure on the gallbladder. In a severe attack the patient suffers the usual symptoms of an acute infection; frank chills, however, are uncommon and the pulse rate is little elevated. One may be surprised at the lack of reaction shown by some patients even when the process has gone on to suppuration; the secondarily infecting organism may, however, be a low grade pathogen. Tenderness in the region of the gallbladder is characteristic. When it cannot be demonstrated, either because of muscle splinting or because the gallbladder lies out of reach of palpation, a thump over the cartilaginous plate may elicit it, or the examiner, from behind the sitting patient, may demonstrate gallbladder tenderness by palpating upwards under both costal margins while the patient inspires deeply. Sometimes one can feel a distended tender gallbladder in the right upper quadrant. Rather less commonly a larger tender mass composed of gallbladder and adherent inflamed omentum may be palpated; it may be very large and extend into the right iliac fossa and since it is often hard and irregular it could be mistaken for a neoplasm.

Abnormal amounts of urobilin, and sometimes bile, are found in the urine. The serum bilirubin is slightly increased and there is usually a leukocytosis.

According to Berk, *empyema of the gallbladder* occurs in 20 per cent of those cases that come to operation; the total incidence, accordingly, would be considerably lower. In our own experience frank empyema is not nearly so common. The patient becomes more ill with increase in fever, local tenderness and leukocytosis, and these manifestations persist instead of clearing up as in the uncomplicated attack. Occasionally the febrile and leukocytic response is slight.

When acute cholecystitis goes on to *gangrene*, the patient becomes gravely ill with increased local tenderness and rigidity, fever, rapid heart rate and leukocytosis. If the gangrenous process is extensive there are signs of peritoneal irritation with marked splinting and pain even on shallow breathing.

Perforation of the gallbladder is an uncommon complication of acute cholecystitis. It may occur gradually, producing a fistula as when a stone erodes its way into the gastrointestinal tract. Rarely it occurs insidiously in patients who have had relatively little tenderness, fever or leukocytosis. Usually it follows upon a very severe attack often associated with local or generalized gangrene. It may be contained by the omentum, by coils of intestine, or by the liver, the latter producing a liver abscess. Free perforation, usually of a gangrenous gallbladder, into the peritoneal cavity is an abdominal emergency which is easily recognized if the patient has been under observation; otherwise, there may be difficulty in differentiating it from perforation of an ulcer or from an acute hemorrhagic pancreatitis. The patient

goes into a state of shock and a spreading peritonitis develops with its concomitant signs. Abdominal distention becomes marked and free fluid may be demonstrated. There is usually a history of former gallbladder disorders and of a recent attack suggestive of acute cholecystitis; one fails to elicit a description of the duodenal ulcer syndrome or of the severe midabdominal pain extending through to the back which is characteristic of hemorrhagic pancreatitis. A diagnostic paracentesis to determine the type of exudate may be helpful; thin sanguineous fluid is suggestive of hemorrhagic pancreatitis and yellow fluid of perforation of the gallbladder. Elevation of the serum amylase is indicative of a pancreatic disturbance which may be merely secondary to the gallbladder disease and, therefore, it is not dependable as a differential test.

That the perforation need not be catastrophic is exemplified by the patient who presented himself, having had a pericholecystic abscess which tracked up over the liver, perforated the anterior abdominal wall, and formed a subphrenic abscess which ruptured through the diaphragm and caused a lung abscess, finally healing itself spontaneously. During an interim in this patient's stormy course the gallbladder was removed. This man has been quite well for a period of over three years.

Mild acute pancreatitis may accompany acute cholecystitis but fulminating hemorrhagic pancreatitis is rare. Cholangitis and septicemia hardly ever occur. A low grade toxic hepatitis is often present but it is not severe and hepatic enlargement is moderate, if present at all.

Differential Diagnosis of Acute Cholecystitis.—*Duodenal ulcer* penetrating into the head of the pancreas is the most common extrabiliary condition confused with cholecystitis. Such patients give the typical history of periodically recurring indigestion which is relieved by food; examination usually reveals tenderness in the right epigastrium, which is lower and less superficial than that of cholecystitis; indeed the tenderness may be limited to the right costomuscular angle. An ulcer will usually be demonstrated by a gastric series.

Acute cholecystitis is sometimes confused with *coronary thrombosis* because the pain in the former may radiate up to the precordium. In coronary thrombosis the pain may extend to the epigastrium, but no splinting or tenderness is present over the gallbladder. There will be other evidences of cardiac disability, frequently including a history of angina pectoris, and usually an abnormal electrocardiogram.

Acute cholecystitis may simulate *appendicitis* if the gallbladder extends down in the abdomen producing marked tenderness and splinting in the right lower quadrant. Careful physical examination and the history of previous attacks of colic usually clarify the picture. Appendicitis may be mistaken for acute cholecystitis if the cecum is very high. The history, again, is of great importance. If doubt persists a barium enema to determine the position of the cecum may be helpful.

Treatment.—The treatment of patients suffering from acute cholecystitis requires a great deal of care and skill. They are best cared for in a hospital because serious complications may develop with little warning. Daily consideration and examination are necessary, particular attention being paid to the clinical condition of the patient, changing physical signs, fever and white blood count.

The important principles of early treatment are rest and relief of pain and dehydration. Should the patient be vomiting, fluids by mouth are withheld and glucose, 5 per cent in physiological solution of saline, is given intravenously. Pain is controlled with sedatives such as morphine, 15 mg. repeated as necessary. Local heat to the abdomen is applied by means of linseed poultices or an electric pad. As soon as the patient can eat, bland foods are given frequently in small quantities and the amount gradually increased, avoiding roughage, raw fruits, vegetables, greasy and fried food; this diet, in fact, is similar to that given to peptic ulcer patients. We believe that conservative treatment in the acute stage leads to lower morbidity and mortality.

The advisability of operation at a later date must be decided upon the merits of each individual case. The determining factors are the severity of the illness, the rate of subsidence, and the frequency of previous attacks, having due regard for the patient's age and general state of health. Operative procedures undertaken in the interval provide the best opportunity for adequate surgical treatment; this consists of removal of the gallbladder and careful exploration of the common bile duct (since stones in the duct occur in about 10 per cent of cases).

Surgical intervention at an early stage of the disease has, however, been advocated. Such a policy may lead to operation on patients who have biliary colic without cholecystitis or on others in whom the diagnosis of biliary disease, based on a short period of observation, is quite wrong. It should be remembered that the patient is rarely seen within twenty-four to forty-eight hours of the onset of the pathological process, and seldom admitted to hospital before symptoms have been present for two days. Thus the theoretical advantages of "early" operation are seldom attainable. Operation in the presence of active inflammation is unsatisfactory and often dangerous. It is then more difficult to remove the gallbladder and unwise to explore the common bile duct. Moreover, there is great danger that the duct may be damaged and a stricture produced. In the presence of acute disease palliative surgical measures are indicated when one suspects frank empyema or gangrene or perforation of the gallbladder in a patient not doing well. A second operation must be undertaken at a later date to remove the gallbladder and any common duct stones.

When a large irregular tender mass is palpable in the right upper quadrant and one suspects that a perforation of the inflamed gallbladder had been contained by omentum and coils of intestine the patient is best treated by conservative measures while watching the patient

carefully. The inflammation subsides, the mass disappears and at a later date satisfactory surgical treatment can be completed in one operation.

Cholesterosis of the Gallbladder ("Strawberry Gallbladder") is an interesting condition, but from the point of view of the clinician it is of concern only in so far as it produces symptoms of cholecystitis. As an entity it cannot be diagnosed with certainty prior to operation. The treatment is that of acute cholecystitis.

Hydrops of the Gallbladder follows upon persistent obstruction of the cystic duct. There is no infection present. It is commonly preceded by attacks of colic. A large smooth distended gallbladder, usually not tender, becomes palpable. It contains mucus which finally becomes clear and colorless. Treatment is by cholecystectomy done at a convenient time.

CHRONIC CHOLECYSTITIS

Chronic cholecystitis is a diagnostic term commonly used to include many symptom complexes. The majority of persons with bloating, belching, heaviness in the epigastrium, dizziness, who may also show an abnormal cholecystogram, are not suffering from disease of the gallbladder. This group includes cases of nervous dyspepsia and psychoneurotic states in general; a very small fraction show food sensitivity, and a few are migrainous. It is unfortunate that cholecystectomy has often been done for chronic abdominal disorders wrongly ascribed to the gallbladder. Many of the patients have demonstrable stones to which their symptoms may be attributed when in reality they are due to other disorders.

Mild chronic upper abdominal symptoms do, however, occur as a result of cholelithiasis and associated gallbladder disease; the relationship is demonstrated by a convincing history of repeated attacks of biliary colic, mild or severe. In the absence of such attacks the diagnosis of chronic cholecystitis is doubtful.

The reflex symptoms are sometimes amenable to medical treatment which consists of a regimen suitable for a duodenal ulcer patient with a bland diet, frequent feedings, and mild sedatives such as 15 mg. of phenobarbitone or 0.6 mg. of nitroglycerine about an hour after meals. Those who cannot be kept comfortable by this method and those who have repeated attacks of colic or cholecystitis should have the gallbladder removed. Occasionally repeated inflammation and scarring results in a virtually spontaneous cholecystectomy with relief of symptoms; the gallbladder may later be found as a scarred fibrous mass containing stones but with little lumen remaining.

It is well known that chronic epigastric distress often persists after cholecystectomy; this may be gassy indigestion due to the reflex motor disturbance persisting long after removal of the gallbladder or may be quite unrelated to the gallbladder disease. In either case, continued

supervision, interest and encouragement must be exhibited by the doctor.

COMMON DUCT STONE

Most stones in the bile ducts are first formed in the gallbladder. In patients with hemolytic jaundice, however, bile pigment stones may form in the common duct; such stones are often tiny and may be passed giving rise to short, sharp attacks of colic. Larger stones may remain in the common duct for a long period, even years, without causing symptoms, although the duct usually becomes dilated. The distinctive features of common duct stone are attacks of colic, jaundice, fever and chills. The colic from common duct stone is similar in character to cystic duct colic, possibly localized more consistently in the epigastrium. Between attacks gassy indigestion may be troublesome.

Jaundice is common, usually transient and variable in degree; when severe it tends to be more persistent. Its occurrence without colic or a history of colic and indigestion is extremely uncommon. Even mild jaundice, especially if prolonged, may be accompanied by itching; at times this is marked. In about one third of the jaundiced patients, chills and fever may be present; the white blood count is then increased and tends to be higher than in uncomplicated gallbladder infections. Sometimes a hemorrhagic tendency develops if the jaundice is long continued. Significant enlargement of the liver is uncommon in the absence of cholangitis. The gallbladder is occasionally palpable, but it is not as large as in carcinoma of the pancreas. Tenderness and splinting may be present also. After repeated attacks of obstruction with cholangitis a biliary type of cirrhosis may develop and both liver and spleen may then be enlarged.

Laboratory findings are often equivocal. The demonstration of moderate or marked hyperbilirubinemia and bilirubinuria confirms the presence of jaundice which in a patient with attacks of biliary colic is suggestive of stone in the common bile duct. The stools become clay colored when the obstruction is more complete and prolonged. Marked elevation of the serum phosphatase, and a normal galactose tolerance test in the presence of jaundice, is indicative of an obstructive lesion. In long-continued jaundice the prothrombin time may be prolonged. Biliary drainage after the attack aids in diagnosing the condition especially if the patient has already had a cholecystectomy, but x-ray investigations are of no value.

Carcinoma of the head of the pancreas, of the ampulla of Vater or of the common bile duct may be confused with duct stone. The jaundice in the malignant conditions is apt to be more continuous, and not associated with as much pain, and there is an absence of a long history of former biliary upsets.

The treatment of choledocholithiasis, once diagnosed, is essentially

surgical. It may be necessary during the acute phase to treat the patient medically as in cholecystitis. In the presence of prolonged jaundice synthetic vitamin K, 5 mg. per day, should be given. Itching is not a problem in jaundice of short duration but when prolonged the pruritus may be intolerable. Operation to overcome the obstruction gives relief but if this cannot be done medical measures must be tried. The application of different solutions usually meets with indifferent success. These solutions include: calamine lotion, with or without phenol, or menthol (1 per cent); saturated solutions of sodium bicarbonate, magnesium sulfate or boracic acid; or vinegar. Mild sedatives such as phenobarbitone in small doses (15 mg.) repeated, or codeine and salicylates, or small doses of bromides may be more useful. Recently we have found that procaine 0.1 per cent solution in 500 to 1000 cc. of physiological saline given slowly intravenously gave temporary relief of varying duration.

Infective cholangitis is the most common complication of stone in the common duct; it is secondary to chronic partial obstruction and occurs also in association with stricture and carcinoma of the ampulla. It may become frankly suppurative producing liver abscesses or pylephlebitis. The patient then becomes quite septic having chills and fever, leukocytosis, and enlargement of the liver with tenderness. Suppurative cholangitis has been encountered also in typhoid fever, pneumococcal and streptococcal septicemia.

The principles of treatment are similar to those followed in acute cholecystitis. Chemotherapeutic agents are not very efficacious because they fail to reach the ducts until the bile flow is established. However, sulfonamides, penicillin or streptomycin should be tried. The bile duct and any complicating abscesses should be drained and the stones removed.

Chronic cholangitis of a catarrhal nature, in the absence of any obstruction of the biliary tree, is possibly a clinical entity, although we have never recognized such a case. It is said to be characterized by the presence of repeated attacks of mild jaundice, slight distress in the upper abdomen and at times mild biliary colic. It is diagnosed by biliary drainage, with the demonstration of deeply bile-stained mucous shreds and detritus. The liver and spleen may be enlarged. It is important to rule out an obstructive lesion before making the diagnosis. The treatment is repeated biliary drainage and administration of bile acids.

BENIGN STRICTURE OF THE BILE DUCTS

Benign stricture of the common bile duct or hepatic duct is usually caused by damage done at a previous operative procedure or by stone; rarely it occurs as a primary scarring process. The resulting obstruction may be partial or complete. The development of the stricture from a stone is gradual, frequently causing a low grade cholangitis

with mild jaundice; at times acute cholangitis with intense jaundice, fever and chills, as mentioned above, may occur. A history of previous biliary colic is elicited in most cases; the latter is important in differentiation from malignant obstruction.

Jaundice from stricture caused by surgical trauma usually develops soon after operation, although it may not appear for several months. Clay-colored stools and excessive drainage of bile from the sinus suggest the presence of traumatic stricture, but the possibility of a persistent stone or a neoplasm at the lower end of the duct must be borne in mind. If the obstruction is allowed to persist the duct dilates proximally even up to the fine radicles of the biliary tree; a biliary cirrhosis with hepatomegaly may result. An attempt to relieve the stricture or at least decompress the overdistended duct should be made.

Other Causes of Obstruction of Common Bile Duct.—Compression of the common bile duct by inflammation or edema associated with a duodenal ulcer, often penetrating, may give rise to jaundice which may be confused with that caused by stone or stricture. Similarly enlarged hylar glands may cause jaundice by compression of the common bile duct. We have never encountered obstruction of the biliary duct by parasites. Carcinoma of the gallbladder and ducts is mentioned later.

BILIARY DYSKINESIA

Biliary dyskinesia is a functional disturbance of the musculature of the biliary tract producing symptoms similar to biliary colic. It may be due to a disturbance in the normal reciprocal relationship between the tone of the gallbladder and cystic duct muscle and that of the sphincter of Oddi. The diagnosis is usually made by exclusion. Sometimes this disturbance in the biliary tree may occur as an expression of the migrainous or psychoneurotic state. In rare instances it may be associated with an intolerance to fats. Mild jaundice may occur. However, experience shows that with the passage of time, the diagnosis frequently proves to be wrong.

This type of disturbance of function is more commonly seen after cholecystectomy, especially in those patients who have had a long disability from recurrent biliary colic and gallbladder infection preceding surgical treatment.

CARCINOMA INVOLVING THE BILIARY TRACT

Primary carcinoma of the gallbladder is unfortunately rather silent in its onset; usually it has become inoperable by the time the patient seeks medical aid. There is a high incidence of associated calculus with carcinoma. The ratio of females to males is four to one. It occurs most often in the sixth decade of life. The growth extends to the liver, and often involves the bile duct, producing jaundice. Empyema of the gallbladder, or hydrops, may occur from cystic duct obstruction.

Pain, usually of a dull, boring type, felt in the region of the gallbladder, is a common symptom by the time the patient seeks medical aid. Tenderness is common, partly due to antecedent vomiting. The diagnosis is suggested by the palpation of a hard, irregular mass in the region of the gallbladder. It is difficult to be sure that this is not part of the liver. Only occasionally has successful removal of the growth been possible, and that by coincidence, when a cholecystectomy was being done for other reasons.

Primary carcinoma of the bile ducts is rare. It occurs more commonly in men than women, usually after 60 years of age. Jaundice is an early and a persistent symptom. If the growth is below the cystic duct, the gallbladder is enlarged and may be palpable. The lesion is seldom differentiated from carcinoma of the head of the pancreas.

Carcinoma of the ampulla of Vater is another variant. (Here there may be interference with the external pancreatic secretion, and some patients have diarrhea.) The pain is often severe, and at times colicky. The jaundice tends to be deep, usually continuous, but the degree may vary. As it is an obstructive jaundice, itching may be intolerable.

Ampullary carcinoma is hard to differentiate from carcinoma of the head of the pancreas, unless the jaundice is variable. On x-ray examination an ulcer crater in the second portion of the duodenum may sometimes be visualized or, on the other hand, a wide swing, or fixation of the medial wall of the duodenal loop may be found in carcinoma of the head of the pancreas.

Surgical treatment of carcinoma of the bile ducts and ampulla is still in the experimental stage.

SUMMARY AND CONCLUSIONS

If calculi were eliminated from the causes of biliary disorders, disease in that tract would be limited almost entirely to carcinomas which are relatively rare. The formation of calculi is metabolic, ill understood, and their incidence increases markedly with age; they are more common in women.

The great majority of the general population who have gallstones have insufficient symptoms from them to produce any complaint of ill health. It is not uncommon, however, that acute and especially chronic gastrointestinal symptoms are wrongly ascribed to the gallstones which may be present, or to a gallbladder in which x-ray studies erroneously furnish the only suggestion of disease. There are many fallacies in the x-ray examination of the gallbladder.

The most distinctive manifestation of biliary calculi is the occurrence of colic. The greatest morbidity and mortality arising from their presence is due to the inflammatory phenomena that follow in their train. The important points in diagnosis have been described. Errors connected with the diagnosis of "chronic cholecystitis" have been stressed.

Proper management of gallbladder disease is difficult and requires nice judgment and foresight. If surgical treatment is considered necessary, proper timing is essential. When stones in the gallbladder give rise to recurrent biliary colic, cholecystectomy is usually advisable but each case should be considered on its own merits. Calculi in the common bile duct should be removed on discovery if operation is not contraindicated for other reasons. In acute cholecystitis medical treatment is indicated; cholecystectomy should be undertaken if necessary, only after recovery from the acute attack at a time when the operation is safer and adequate exploration of the common bile duct is feasible.

Carcinoma of the gallbladder causes no early symptoms and is seldom recognized in time for consideration of radical removal. It is often mistaken for secondary carcinoma of the liver. Carcinoma of the common bile duct, or of the ampulla, causes jaundice early and accordingly radical resection may sometimes be attempted; such measures are, however, still in the experimental stage.

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CHRONIC HEPATITIS. THE CIRRHOSES

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CIRRHOSIS of the liver, although not a common disease, is one which has engaged the interest of the clinician and experimental pathologist for many years. This interest has been greatly enhanced during the past decade by the illuminating results of animal experiments and by the improvement in the prognosis of human cases brought about by the application of the therapeutic concepts of Patek.[1,2]

Originally the term cirrhosis was applied by Laënnec to a condition that apparently was an example of what we would now call "portal" cirrhosis. Since that time the scope of this term has become broadened and it is now applied to other forms of chronic hepatic disease in which there is a diffuse fibrosis. The varieties of cirrhosis which may be encountered are given in the following classification.

CLASSIFICATION OF CIRRHOSIS

A. *Portal Cirrhosis*
   1. Ordinary portal cirrhosis. Liver may be large or small. Fatty cirrhosis.
   2. Postnecrotic cirrhosis ("toxic" cirrhosis).
   3. Pigmentary cirrhosis (hemachromatosis).

B. *Biliary Cirrhosis*
   1. Primary biliary cirrhosis.
      (*a*) Intrahepatic cholangitic or cholangiolitic biliary cirrhosis (Karsner[3]).
      (*b*) Primary xanthomatous biliary cirrhosis (Thannhauser[4]).
   2. Secondary biliary cirrhosis.
      Secondary to chronic long-standing partial obstruction of the extrahepatic biliary ducts with or without infection. Usually caused by traumatic stricture or impacted gallstone.

C. *Congestive Cirrhosis* ("Cardiac" Cirrhosis).

D. *Syphilitic Nodular Cirrhosis.*

For practical purposes this classification is reasonably satisfactory. It has the disadvantage that it is partly descriptive and partly etiological. Recent animal experimentation would indicate that cirrhosis of the "portal" type in many cases has a nutritional etiology but as

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this is not true of all cases we have preferred to retain the classical term. Of all the cirrhoses mentioned in the above classification the variety known as ordinary portal cirrhosis is by far the most common and most important and the remarks which follow will be largely confined to a discussion of this disease.

PORTAL CIRRHOSIS

Ordinary Portal Cirrhosis. Fatty Cirrhosis.—Because it is generally thought that so-called fatty cirrhosis is merely an early stage in the development of certain cases of ordinary portal cirrhosis the two conditions will be discussed together.

Etiology.—It is important, as Moon[5] and others have suggested, to have the conception that cirrhosis is the result of a chronic hepatitis. Any influence which produces chronic diffuse injury to the hepatic cells will result in some degree of fibrosis. The degree and character of this injury may vary but the characteristic results of it are (1) degeneration and destruction of liver cells, (2) regeneration of liver cells from those that have escaped destruction and (3) proliferation of connective tissue. This process is usually a slow one and it may take years for it to reach a stage that produces clinical symptoms. It is possible then that, if it can be recognized in its early stages, adequate therapy may arrest the progress at a time when the liver is still capable of fulfilling its many functions.

A full discussion of all the possible etiologies of portal cirrhosis is beyond the scope of this paper. However, in view of the recent evidence both experimental and clinical, which suggests that portal cirrhosis has as its basis a nutritional deficiency, it is necessary to see just how far this conception can be applied to the human disease. This is of extreme importance because if this can be substantiated it affords a sound basis upon which to employ rational therapy.

As indicated above, any condition which will produce chronic injury to the liver cells will result in some degree of fibrosis. One such injurious mechanism seems to be chronic fatty infiltration of the liver, a condition which may result from a number of causes including certain nutritional deficiencies.

It was noted first by Allan and his coworkers,[6] in 1924, that dogs made diabetic by complete pancreatectomy but kept alive by the use of insulin developed extensive deposits of fat in their livers if they were not given raw pancreas by mouth. In 1937 Chaikoff and his associates,[7,8] observed that animals with such fatty livers showed in addition evidence of increasing hepatic fibrosis if they were kept alive for a sufficient length of time. Of sixteen such animals living for 2.6 to 5.5 years after pancreatectomy, eight showed fibrosis and four of them showed well advanced portal cirrhosis of the liver. By the time that the most severe fibrosis had become apparent the fat had largely dis-

appeared so that there was no evidence that fatty infiltration had preceded the fibrosis. In 1940 these same workers,[9,10] showed that similar changes could be produced in the livers of normal dogs when their livers were kept excessively fatty by the continued administration of a high fat diet. Because of these observations they suggested that a high fat content of the liver was an important factor in the production of cirrhosis. They felt that the presence of the large amount of fat in the liver maintained over a long period of time caused a low grade injury to hepatic cells and produced as a result a diffuse proliferation of fibrous tissue which in some animals at least was sufficiently marked to give rise to a lesion resembling that seen in portal cirrhosis. As a result of these observations on dogs, Connor[11, 12] suggested that so-called "alcoholic" cirrhosis in man is probably caused by the chronic fatty infiltration of the liver that is so often found associated with the excessive use of alcohol.

The observation of Allan's group noted above has been followed, largely through the work of Best and his coworkers,[13] by the development of the conception that fatty infiltration of the liver is prevented under ordinary circumstances by the presence in the normal diet of certain essential substances which he has named *"lipotropic factors."* This lipotropic activity, first shown to be possessed by raw pancreas, was later found to be a property of crude lecithin[14, 15] and then of purified choline,[16] one of the constituents of lecithin. Soon afterwards it was reported from the same laboratory[17] that certain proteins, notably casein, acted in a similar manner. This lipotropic activity of protein was shown subsequently by Tucker and Eckstein[18] to be due to the presence in the protein molecule of the amino acid methionine which is able to serve as a choline precursor. When diets lacking adequate amounts of such lipotropic factors are fed to animals for a prolonged period of time there occurs not only an excessive accumulation of fat in the liver but also a proliferation of fibrous tissue which ultimately progresses to a cirrhosis of the portal type.[19-27] After these changes have been so produced the administration of supplements of choline, methionine or casein has been shown to cause a rapid disappearance of the fat, and a considerable hyperplasia of the parenchymal cells of the liver.[27, 28, 29]

Although no definite decrease in the amount of fibrous tissue was noted as the result of such treatment in the experiments just described it has been shown that moderate degrees of hepatic fibrosis produced by such an agent as carbon tetrachloride may diminish considerably when the administration of the toxic material is stopped.[30, 31]

Sellers[32] working with rats in Best's laboratory has recently been able to show that this improvement in carbon tetrachloride cirrhosis is dependent upon the presence of adequate amounts of choline in the diets fed to the experimental animals. If animals with such a lesion were given diets which were deficient in lipotropic materials the im-

provement in the cirrhosis did not occur. When choline was added to such faulty diets not only was there disappearance of fat and regeneration of parenchymal cells, but there was also a striking diminution in the amount of fibrosis so that the liver returned almost to normal. The choline could be supplied as the chemical itself or as one of its precursors, methionine or casein. Choline is therefore an essential dietary constituent, seemingly necessary for growth and repair of tissue as well as for its lipotropic action.

Just what part *dietary deficiencies* or the absence of lipotropic factors may play in the development of human cirrhosis is not clear, but the observations concerning the high incidence of cirrhosis in countries such as India, Ceylon, Syria and China, where the diet is notoriously poor in vitamins and first class protein[33, 34] and where alcoholism is not a factor, suggests strongly that in these countries at least there is a connection between faulty nutrition and cirrhosis. The observation[35] that a significant number of cirrhotic patients also show other evidence of vitamin and nutritional deficiencies, including peripheral neuritis and frank pellagra, lends support to the theory that some cirrhoses at least may have a nutritional origin.

Even more convincing is the evidence published by Gilbert and Gillman[36] from South Africa. In certain regions in this country the income of the native blacks is very low. They are forced, for this reason, to live on the cheapest available carbohydrate food—partly cooked corn meal—supplemented in some cases by small amounts of fermented cow's milk. Meat is a luxury with these people and is eaten only on ceremonial occasions or when the cattle die of starvation. Their diet is thus grossly deficient in proteins and in vitamins and as a result deficiency diseases of all kinds are widespread. What is important, from the point of view of the present discussion, is that cirrhosis of the liver is present in some four-fifths of the male population who come to autopsy. These workers[37, 38] have also shown that young rats which are fed on such a diet develop in time fatty livers and eventually hepatic lesions which resemble portal cirrhosis thus by these observations adding considerably to their evidence that, in these people, there is a close relationship between deficient diet and hepatic disease.

In every series of cases of cirrhosis reported there is a large proportion (30 to 80 per cent) that give a history of *alcoholism* and it is generally felt that chronic alcoholism is a very important predisposing factor in the development of portal cirrhosis, so that from time immemorial the two conditions have been linked together. The death rates in various countries from alcoholism and cirrhosis run parallel one with the other. Experimentally, however, it has not been possible to show that ethyl alcohol can by itself produce cirrhosis and it is common experience of course that there are many alcoholics who do not develop this condition. However, those people who are given to

repeated episodes of excessive drinking often undergo during these bouts complete or partial starvation except for the calories derived from alcohol. Even during the periods of relative sobriety, their appetite is so poor that the food intake is greatly limited, particularly in regard to those dietary factors such as protein and vitamins which have been shown to play such an important part in the prevention of cirrhosis in animals. It is well known that such individuals may develop tremendous fatty infiltration of the liver, probably because of deficient intake of lipotropic materials, and it seems justifiable to expect, as Connor[11] has proposed, that if such fatty infiltration persists or is frequently repeated, it will lead, as it does in animals, to a definite cirrhosis. It has not been uncommon in our experience to find in alcoholic patients admitted to hospital following a period of heavy drinking, a large distended liver. With rest in bed and the administration of a well balanced diet (which will probably contain adequate amounts of lipotropic factors[39]) such a liver often diminishes quite rapidly in size. In some cases it appears to return completely to normal. In others, although becoming smaller, it remains enlarged and firm. We have not performed needle biopsies on our patients but reports from other clinics[11, 12, 40, 41] and the autopsy examinations of our own patients who have died, lead us to believe that the liver (on admission) was distended with fat. With treatment the fatty infiltration disappears to leave a relatively normal liver if there is little residual fibrosis or a firm fibrotic liver containing little fat if the cirrhotic process is well established.

Although it is evident that in any group of patients suffering from portal cirrhosis the incidence of alcoholism is high, it is also just as evident that there is a group of patients in each such series where alcoholism and the resulting nutritional deficiencies have not been factors. In this latter group the possibility has to be explored of course, that defective diets, not associated with alcoholism, may have been responsible for the appearance of the cirrhotic process. Because the matter is of more than mere academic interest we have attempted to obtain, by a detailed study of the dietary history, some indication of the part that inadequate nutrition may have played in the development of cirrhosis in our patients.

This dietary history should cover the patient's life for a considerable period before the onset of symptoms because anorexia and diminished food intake are often manifestations of an early established cirrhosis. To be complete, such an enquiry should extend to the growing period as well, for as Gillman and his associates[38] have shown, the effect of inadequate diets may be more serious in growing individuals than it is in adults. Often, of course, such information about the patient's diet is very difficult to obtain and when obtained is of doubtful accuracy, but one should attempt in this way to obtain as good an idea as possible of the general nature of the food intake.

The number of patients that we have been able to study in this way is too small to allow us to draw any final conclusions, but it can be said that, of the forty patients with portal cirrhosis seen during the past two years, less than half of them can be described as suffering from chronic alcoholism. Of the remainder, many were total abstainers and the others were accustomed to take only an occasional glass of beer, wine or spirits, an amount no more than that habitually consumed by a large proportion of the general population. In only a few of the nonalcoholics was it possible to obtain evidence that the diet was so inadequate that it might even be considered to have any etiological relationship to their cirrhosis. In the others we were able to satisfy ourselves that their diet had always been good and had always contained adequate amounts of first class proteins, vitamins and other essential food factors. Such cases must be considered to have some other etiology. We have enquired diligently into the past history of such patients, searching for other possible etiological factors such as previous attacks of acute infective hepatitis, or exposure to toxic drugs or chemicals which are known to harm the liver, but in most cases it has not been possible to recognize any such cause.

It is possible that in some of these patients there is an *interference with the production or flow of the external secretion of the pancreas.*[39] Such a defect might interfere with the adequate liberation from the food of choline or its precursors and this seems to be an etiological factor in the cirrhosis associated with chronic cystic pancreatitis.[42] This possibility has not been entirely eliminated in those of our patients who have no recognizable cause for their cirrhosis, but they have not exhibited any other manifestations that would suggest such a lesion.

The possible relationship of *acute hepatitis of virus origin* to cirrhosis has not been settled. It is known that the great majority of patients who have acute infective hepatitis make a perfect clinical recovery and that histological examination of the livers of recovered patients has shown complete restoration of the hepatic parenchyma.[43] It is true that occasionally one encounters a patient with cirrhosis in whom the pathological process seems to have begun with what appeared to be an attack of acute infective hepatitis. Although recovery from the jaundice occurs, the liver remains enlarged and firm and other evidence of chronic hepatitis persists. One should not lose sight of the possibility that in some of these patients the cirrhosis may have been present before the onset of the acute hepatitis. In others, too, jaundice may have been a manifestation of an already established cirrhotic process rather than the result of a virus infection of the liver.

Pathology.—The pathological changes which are present in the liver of a patient with cirrhosis will depend upon the stage of the process and upon the relative amount of degeneration and regeneration of the parenchymal tissue, the extent of fibrous tissue proliferation, and the

kemias and similar blood dyscrasias, Hodgkin's disease and other causes of hepatic enlargement can usually be eliminated by the appropriate investigations.

In this type of case, as well as in those in which the diagnosis is more obvious, certain liver function studies are often of considerable value. The presence of excess amounts of urobilinogen in the urine, and of increased levels of bilirubin in the serum, in cases where there is no evidence of increased blood destruction, suggests hepatic dysfunction. An abnormal retention of bromsulfalein is nearly always shown by patients with cirrhosis although in the early or less marked cases this retention may be very slight. A mild to moderate elevation of the alkaline serum phosphatase is usually found in these patients as well. Abnormalities of the serum proteins which are characteristically found in portal cirrhosis[44] can be recognized by such tests as the cephalin-cholesterol flocculation, thymol turbidity, Takata-Ara and formol gel tests and more accurately by fractionation studies employing salting out or electrophoretic procedures. The finding of an abnormal protein known as the "13½ per cent fraction,"[44] which can often be either demonstrated qualitatively or determined quantitatively in the serum of such patients, although certainly not diagnostic of cirrhosis, is often very suggestive. Although considerable help may be given by such tests it must be remembered that they may be misleading and that the making of a correct diagnosis must always depend upon a careful assessment of all the clinical and laboratory findings.

More recently in certain clinics the accuracy of the clinical diagnosis has been increased by microscopic examination of specimens of liver obtained by needle biopsy. Although such pathological examination of a diseased liver enables one to make a definite diagnosis and allows one to determine the stage of the process and the response to treatment, it is not a procedure which should be undertaken without due regard to the dangers involved. It is well to remember that even in the hands of competent workers this examination gives rise to occasional complications and is associated with a small but definite mortality.

Treatment.—Until the advent of Patek's report[1] in 1937 it was customary to treat most patients with cirrhosis with a high carbohydrate, low protein, low fat diet. Patek, impressed by the nutritional deficiencies exhibited by many of these patients, prescribed a diet high in protein, calories and accessory food factors. In addition to this dietary program he gave brewers' yeast by mouth and administered concentrated liver extract and thiamine hydrochloride by injection. In assessing his results[2] he was careful to state that the favorable responses observed in some of his patients gave no indication as to whether the extra protein, vitamin B concentrates or some unknown substance was responsible for the observed improvement.

Fleming and Snell[45] also used a high protein diet supplemented by

the addition of vitamins, oral liver extract and yeast but, because the work of Bollman and Mann[46] had shown that ascites in cirrhotic dogs was exaggerated by the feeding of meat or meat extracts, they advised that most of the protein used should be given in the form of milk, egg whites and vegetables. Many subsequent workers, however, have felt that it was not necessary to limit the meat in the diet for such experimental reasons, and as meat is an excellent source of first class protein it has since been used freely in the treatment of patients with cirrhosis.

Because of the apparently successful application of the use of choline and other lipotropic factors to the prevention and treatment of experimental cirrhosis in animals,[10-20] many investigators have employed such agents in the treatment of the human disease.[47-60] In spite of the apparent success obtained by some of these, there is no unanimous agreement as to the beneficial action of these materials. One of the difficulties encountered in evaluating such treatment is the fact that the high protein diets usually employed already contain a moderate or high, but uncertain, amount of choline and its precursors. Also, the wide variety of therapeutic measures employed, in addition to the use of choline in the treatment of these patients, has made it practically impossible to judge the value of any single agent.

The assessment of the value of any form of therapy in this disease is extremely difficult. The stage of the cirrhotic process in any given case is obviously one very important factor which will determine the success of treatment. One might expect, in cases where the liver is large and fatty with little fibrosis, as it is in the early stage of alcoholic cirrhosis, that the administration of lipotropic factors would be followed by a decrease in the fat content and by a return of the organ to more normal size. A proportion of such patients show jaundice and ascites but even these manifestations may disappear as the amount of fat in the liver is decreased. Adequate amounts of lipotropic factors are likely to be supplied by the feeding of a well balanced diet, particularly if this diet contains normal amounts of first class protein such as that found in meat, eggs and milk products. In the majority of cases of large fatty liver associated with alcoholism good results will probably be obtained by rest and the administration of a highly nutritious high protein diet alone. However, to ensure the presence of sufficient amounts of the necessary nutritional substances it is desirable to reinforce such a diet with supplements of skimmed milk powder and brewers' yeast.

The adequate therapy of early cirrhosis of alcoholic origin must include not only the immediate and intensive treatment of the condition, but also strenuous efforts to combat the alcoholism, the real underlying cause of the disorder. The immediate therapy should consist of bed rest with suitable sedation if necessary and a dietary regimen which supplies a high caloric, high protein, high carbohydrate intake.

At the Toronto General Hospital the routine diet given to such patients contains 400 gm. of carbohydrate, 70 gm. of fat and 145 gm. of protein. Sixty-five grams of the protein are given in the form of skimmed milk powder and brewers' yeast, thus ensuring an adequate supply of first class protein and of lipotropic factors. Care must be taken to ensure that not only is such a diet prescribed, but also that as much of it as possible is eaten. Adequate nursing care at this stage is invaluable. A protocol should be kept so that the amount of food actually consumed is known. If it becomes evident that the patient is unable to take an adequate amount of food by mouth it will then be necessary to supplement the diet with concentrated duodenal tube feedings.

The period of rest should be prolonged until the maximum favorable response has been obtained. The duration of this period will vary considerably with the individual patient. With such treatment a decided improvement has been observed in a number of patients with early cirrhosis and fatty infiltration, as judged by a return of their sense of well being, the disappearance of jaundice, the diminution or disappearance of ascites and edema, an increase in the level of the serum albumin and a definite decrease in the size of the liver.

After discharge from hospital it is essential that these patients continue to take a diet similar to that outlined above and that they be under periodic medical supervision. It is essential, too, that they abstain entirely from all alcoholic beverages. In this they may be helped considerably by encouragement and psychotherapy. Unfortunately the almost complete inability of these patients to avoid further excesses minimizes to a great extent the probability of their complete and lasting recovery.

As has been pointed out earlier in this paper, a fair proportion of patients with symptomless cirrhosis are encountered in whom neither alcoholism nor dietary deficiency has been a factor. It has seemed desirable in such patients to employ a similar type of treatment with the addition in certain cases of choline in amounts up to 4 gm. daily, but up to the present even prolonged therapy seems to have produced little improvement in these patients. The size of the liver has remained unaltered and the low level of the serum albumin has persisted.

In the later stages of the disease, where there is marked fibrosis and gross distortion of the hepatic architecture, it is unlikely that any form of therapy can do more than relieve the discomfort of the patient and delay for a varying period the inevitable end. However, in these as well as in the less severe cases, adequate rest and the feeding of a highly nutritious, high protein, high carbohydrate diet, supplemented if necessary by duodenal feedings or intravenous glucose, would appear to be desirable. The value of the addition of choline and other similar materials is as yet undetermined. Specific vitamin therapy is of course indicated for any demonstrable deficiency, but

aside from this there would appear to be little justification for the intensive use of multivitamin preparations. The administration of liver extract to patients with definite macrocytic anaemia would seem to be warranted but, as Jones and Volwiler[11] have pointed out, there does not seem to be enough data to justify the use of crude liver extracts in cirrhotic patients for the purpose of producing diuresis.

In combating edema and ascites the sodium content of the diet should be restricted to the limit of palatability but fluids up to 1500 cc. daily may be permitted. When necessary, weekly or biweekly injection of mercurial diuretics preceded by a twenty-four hour or forty-eight hour course of ammonium chloride is often efficacious in controlling the accumulation of fluid. The intravenous injection of human serum albumin solutions has been shown to be effective in raising the serum protein levels and decreasing the edema but the cost of this therapy is prohibitive and therefore at the moment quite impractical. As the removal of ascites always entails the loss of a considerable amount of body protein, paracentesis should only be done when the patient has become very uncomfortable and other measures have failed to relieve the distention.

Blood transfusion is clearly indicated in the treatment of severe hemorrhage from an esophageal varix and occasionally when a marked anemia has failed to respond to other methods of treatment.

Certain operative procedures are occasionally undertaken in carefully selected cases. The injection of a sclerosing agent into esophageal varices and the establishment by various methods of a portal-caval shunt have been used in certain clinics. Time will decide their value.

Postnecrotic Cirrhosis ("Toxic" Cirrhosis).—The term postnecrotic cirrhosis[3] is perhaps to be preferred to the older term "toxic" cirrhosis because it refers to the condition of the liver found in patients who have recovered, in part at least, from acute or subacute hepatic necrosis. Extensive hepatic damage in these cases is followed by the processes of repair which are characterized by the formation of dense bands of fibrous tissue and by the appearance of hyperplastic nodules of regenerated liver cells. The underlying process—hepatocellular injury—although much more acute and severe, would seem to be not unlike that which is responsible for the occurrence of ordinary portal cirrhosis. Indeed, as Karsner[3] points out, although typical cases of the two conditions are easily separated, "there are borderline cases in which a positive differentiation cannot be made." For the purposes of treatment and management it is felt that these cases should be handled in the same way as those with portal cirrhosis and they are therefore included in this broad general group.

Pigmentary Cirrhosis (Hemachromatosis).—This is a relatively uncommon hepatic disease in which a portal cirrhosis is associated with widespread deposition of the iron pigment hemosiderin not only in the liver but in the pancreas, skin and other tissues. The cause of

the deranged iron metabolism is quite unknown but it seems likely as suggested by Watson[51] that the cirrhotic changes in the liver are secondary to hepatic injury caused by the presence of the high concentration of iron pigment in the organ. The combination in any given patient of skin pigmentation shown to be due to hemosiderin with an enlarged very firm liver and evidence of diabetes mellitus, forms a symptom complex that makes the diagnosis of the typical case fairly easy. However, it should be borne in mind that all these manifestations need not be present and Sheldon[52] has shown that even the characteristic ones may be absent in a small proportion of cases. Jaundice and other signs of hepatic failure are not common.

No treatment is known which will influence the course of the disease and therapy must be directed chiefly towards the control of the deranged sugar metabolism. Whether or not the dietary measures employed in the treatment of ordinary cirrhosis—modified as they must be by the presence of diabetes—are of value in the treatment of this condition has not as yet been determined. Certainly there has been a marked improvement in prognosis since the discovery of insulin has permitted the proper control of the coincident diabetes.

BILIARY CIRRHOSIS

Two types of biliary cirrhosis are encountered. In one of these—primary biliary cirrhosis—the essential lesion is within the liver itself. In the other, or secondary form, the hepatic fibrosis is secondary to some form of extrahepatic obstruction.

Primary Biliary Cirrhosis.—This is a condition which is characterized by chronic jaundice of mild to moderate or even of severe degree not associated with other evidence of marked hepatic insufficiency nor with any obstruction of the extrahepatic bile ducts. It has been called by a number of different names such as chronic intrahepatic obliterating cholangitis, cholangiolitic cirrhosis, hypertrophic biliary cirrhosis, and intrahepatic cholangitic biliary cirrhosis. We have preferred the last mentioned term which is the one employed by Karsner.[3] The pathological process is one in which a diffuse chronic inflammatory process in the portal areas accompanied by fibrotic changes apparently results in a diffuse obstructive lesion of the finer bile passages within the liver itself. In other words, the condition is one of obstructive jaundice in which the obstruction is not associated with an extrahepatic lesion such as gallstones or pancreatic neoplasm but rather with a diffuse chronic hepatitis.

The etiology of this type of cirrhosis is obscure. Certainly neither alcoholism nor nutritional deficiencies seem to play any part. It is possible, as Watson[51] has suggested, that this condition may be one of the sequels of acute infectious hepatitis but the few cases that have been encountered in our clinic do not seem to have begun in this way.

The onset is usually insidious and is not infrequently heralded by

the occurrence of an unexplained pruritus. The patient may have experienced occasional periods of fever and at times attacks of right upper quadrant pain. He may have noticed that his urine was darker than usual and then he becomes aware that his skin and sclerae are somewhat jaundiced.

Examination of the patient reveals a mild or moderate jaundice, a large firm relatively smooth liver and often a palpable spleen. Usually the telangiectases, so characteristically seen in portal cirrhosis, are absent and there is no evidence of ascites or edema. The urine may show both bile and urobilin and the stools may be normal in appearance or somewhat lighter than usual.

The liver function tests usually reveal results which are characteristic of obstructive jaundice and indicate little evidence, in the early stages at least, of hepatocellular damage. There is a variable elevation of the serum bilirubin and frequently a marked retention of administered bromsulfalein. The serum cholesterol may be elevated to 500 or 600 or even to 1000 mg. per 100 cc. and the alkaline serum phosphatase is markedly increased. On the other hand, the galactose tolerance test and the hippuric acid test show little abnormality and there is very little disturbance in the serum protein picture as shown by the cephalin-cholesterol flocculation and formol gel reactions or by fractionation studies.[44] The results of these tests may cause a diagnosis of extrahepatic biliary obstruction to be made unless the possibility of the presence of this type of cirrhosis has been considered and the significance of the large liver and palpable spleen is borne in mind. Indeed, the picture may be so confusing at times that the diagnosis can only be settled by an exploratory laparotomy.

The disease runs a slowly progressive course, sometimes with exacerbations and remissions and mild cases may go on for years. Ultimately a stage is reached at which ascites and evidence of hepatic insufficiency occur and the patient may die from advanced liver failure or from some intercurrent illness.

No form of therapy has been shown to be effective in arresting the progress of the disease. On purely empirical grounds we have employed the same dietary program in these patients as in those with portal cirrhosis. One of the most difficult symptoms to alleviate is the itching. Sedatives and the anti-histamine drugs are of little use but should be tried. Application of bland lotions such as those containing calamine may give some relief. Ergotamine tartrate, although often effective, should never be used for this purpose in these patients because of the very real danger of causing peripheral gangrene.[53]

Some, but by no means all of these patients, exhibit various forms of xanthomatosis and it is possible that the cases which have been called primary xanthomatous biliary cirrhosis[4] properly belong in this group.

Secondary Biliary Cirrhosis.—Moderate degrees of cirrhosis are

DISEASES OF THE PANCREAS

K. J. R. WIGHTMAN, M.D., F.R.C.P.(C)*

IN discussing diseases of the pancreas, reference will be made chiefly to the disorders affecting the exocrine part of the gland and the problems of diabetes and islet cell tumor will be mentioned only incidentally. The first portion of the paper will deal with basic anatomical, physiological and pathological features which may have a bearing on the production or course of pancreatic disease; the various clinical entities will then be discussed with reference to that background.

APPLIED ANATOMY AND PHYSIOLOGY

The anatomical features which should be recalled are the relationship of the pancreas to the peritoneum, the bile duct, the duodenum, the splenic vein, the mesenteric vessels, the renal apparatus and certain nerves. The peritoneum covers the body and tail of the pancreas and is separated from the head of the organ by the duodenum and root of the mesocolon. Thus, inflammatory or neoplastic processes in the tail become disseminated through the peritoneal cavity, while those in the head tend rather to involve the duodenum or the bile duct either by compression or by continuous extension. The splenic vein drains blood from the body and tail of the pancreas through short tributaries which enter it at right angles. Thus, it may either contribute to the extension of disease to the liver or become obstructed and lead to a train of changes of its own. The mesenteric vessels may also become involved. Renal involvement, either through interference with the vessels to both kidneys or with the left kidney pelvis and ureter, is rarely severe but frequently is sufficient to produce changes in the urine. Secondary renal changes are also produced if a profound constitutional upset accompanies the pancreatic disease. The adjacent nerves include the celiac plexus, immediately behind the pancreas, and the somatic nerves of the posterior body wall, whose functional characteristic seems to be that they produce a poorly localized type of pain of a nonspecific character. Thus we find that pain is a common and early symptom of all types of pancreatic disease but that it has no uniformity in character or distribution, other than a tendency to be constant and boring and to radiate to the back. Left-sided pain is more commonly due to pancreatic lesions than to other causes, but this is not of great clinical importance. In general, the pain spreads

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over a wider area than that produced by smooth muscle colic. The development of shock as a complication of acute pancreatic disease has been attributed to involvement of autonomic nerves, but other factors are included as well.

The anatomy of the pancreatic duct has been studied intensively, especially with regard to its relationship with the bile duct. It appears that in more than 20 per cent of people the two ducts are completely separate, in 20 per cent a common channel of significant length is formed, and in the remainder the ducts join together in such a way that simultaneous obstruction of both may occur, with little possibility of producing a "common channel" to allow reflux of secretion from one to the other. These studies have failed to throw much light on the pathogenesis of pancreatic disease except in isolated cases. The lymphatic drainage of the head of the pancreas is to subpyloric lymph nodes, while the body and tail are drained to nodes along the borders of the gland and thence through various channels. These points are of some significance in determining the spread of carcinoma. It has also been pointed out that lymphatics from the gallbladder, after passing through a node at the cystic duct, go down in close relationship with the head of the pancreas to nodes which lie behind it. The importance of these structures in the spread of infection or disease of other types from one organ to the other has not been established.

On the physiological side, it is probably important to note that the pancreatic juice is secreted at a variable rate and with a variable content of enzymes; it is modified in response to different types of stimulus, and is greatest in amount two or three hours after meals. The amount of secretion appears to be in excess of the requirement, for a very gross reduction is necessary before symptoms of pancreatic insufficiency are produced. Therefore, this syndrome appears only as a late and rare complication of pancreatic disease. Smaller degrees of functional impairment may be detected by collecting duodenal juice (with care to exclude gastric secretions) before and after stimulation with secretin, mecholyl, pilocarpine, or by substances injected into the duodenum. The chemical analyses involved are difficult and only gross changes can be interpreted as indicating either widespread, severe disease in the pancreas or obstruction of its duct. It has been suggested that minor changes in endocrine function may accompany diseases of the exocrine portion of the gland with a frequency heretofore unsuspected by most people. The difficulty in interpreting such changes in the presence of serious metabolic disturbances, and without knowledge of the patient's previous behavior in that regard, largely vitiates the usefulness of such investigation. It is surprising how well the function of the islet cells is maintained even in the presence of gross disease, although definite alterations do occur at times.

Experimental obstruction of the pancreatic duct has been found to

cause a rise in the amylase and lipase content of the blood, presumably because these enzymes are absorbed from the damaged pancreas. The serum amylase test, which is used clinically, is derived from this observation and will be discussed in a later section.

The application of these facts to the pathogenesis and treatment of pancreatic disease has not been very helpful. It is commonly stated that acute pancreatitis is prone to occur at periods of increased activity of the gland but, in our series of cases, this has not been observed. In treating the condition one's aim is to reduce the amount of secretion; the patient is not allowed to eat, and the passage of acid from the stomach is minimized by continuous aspiration. This may also help to prevent the occurrence of ileus. In addition, one must provide fluid and salt parenterally. The suggestion has been made that glucose, administered intravenously, is a stimulant to pancreatic secretion and so may be harmful, a possibility that warrants further investigation. The use of morphine for the relief of pain in this condition has been criticized on the basis that it may cause constriction of the sphincter of Oddi and so tend to aggravate the process. Direct evidence on this point is lacking, but it may be advisable to use atropine as well or to substitute one of the newer analgesics. In later stages, or in the presence of chronic disease, it is desirable to reduce the total requirement for pancreatic secretion when there is evidence of insufficiency and to prevent overstimulation of the remaining portions of the organ. This is best accomplished by a diet which is low in fat, with no large meals and no alcohol.

PATHOLOGICAL CONSIDERATIONS

The pathological reaction of the pancreas in acute affections of various kinds is rendered uniform by the presence of trypsinogen in its secretion, since this enzyme readily becomes activated and by digestion of tissue produces edema, necrosis and hemorrhage. The condition may then become self-perpetuating and progressive, even if the original stimulus has been removed. Widespread tissue destruction and hemorrhage make it difficult to work out the sequence of events, and prevent identification of the initiating factor in most cases. It is probable that the disease may be produced in numerous ways and, indeed, every conceivable hypothesis appears to have been explored and supported in various quarters.

The fundamental problem appears to be the means whereby trypsinogen becomes activated to form trypsin. Within the ducts, this may result from reflux of duodenal contents (containing enterokinase) or of bile. It may also occur spontaneously or as a result of infection. The active enzyme then reaches the interstitial tissues by digesting the ducts. On the other hand, it has been shown that, if unaltered trypsinogen gains access to the tissues because of rupture of the smallest ducts and acini (due to increased pressure), it will become

activated there and reproduce the lesion. Thus, pancreatic necrosis may arise through the operation of factors entirely within the gland in some cases, and with the participation of extraneous influences in others.

The amount of damage produced depends on the volume of juice which escapes, the concentration of enzymes in that juice, and the number of large blood vessels with which it happens to come in contact. In some cases only transient edema is produced. In others, massive necrosis with hemorrhage develops with involvement of neighboring structures. Progression of the lesion may be continuous or intermittent, and it may become arrested at any stage. Secondary infection may supervene, producing a suppurative process which may lead to abscess formation. The peritoneum of the lesser sac becomes involved, sometimes with the production of a large effusion which may extend into the general peritoneal cavity. The necrotic material may become liquefied, giving rise to a cavity which forms a pseudocyst lined with fibrous tissue and containing enzymes in its fluid. As this becomes larger, it may discharge its contents spontaneously into the lumen of the bowel or into the peritoneal cavity. In the absence of any of these complications, the necrotic tissue is removed and regeneration of the acinar tissue may occur but a certain amount of fibrosis always takes place.

Extreme fibrosis with reduction in the amount of glandular tissue, distortion of the ducts and the formation of cysts characterize the condition known as chronic pancreatitis. In some cases the history suggests that these changes have been produced as a result of repeated attacks of acute pancreatitis. In others, the clinical course suggests that the lesion has been steadily progressive. The fibrosis may be coarse and interlobular or fine and intralobular, just as in the liver. Calcification, either within the gland substance or in the ducts, is a common late sequel which may be related to the release of lipase. The causative factors are not known, but it is frequently associated with chronic gallbladder disease. Cholelithiasis occurs in more than half the patients with pancreatic disease as compared with an incidence of 10 to 20 per cent in normal people of comparable age groups. The connecting mechanism, if any, has not been identified. It must be remembered that pancreatic disease of various types may be found in the absence of any biliary lesion, and it should be emphasized that the presence of a stone in the gallbladder does not necessarily indicate that the bile is infected. The suggestion has even been made that pancreatic disease may predispose to gallbladder disease, rather than the reverse.

True cysts and benign neoplasms are rare and produce symptoms only if they interfere with neighboring organs. Excess insulin production, in the case of benign tumors of the islet tissue, leads to a special train of symptoms. The natural course of malignant neoplasms of the

pancreas is determined largely by anatomical factors, which will be noted later in the clinical discussion.

GENERAL CLINICAL CONSIDERATIONS

When one comes to examine the relationship which these basic factors have to the clinical syndromes, one finds many difficulties. For example, the constant, boring epigastric pain which radiates through to the back is easy to understand, yet it is hard to account for discontinuous or variable pain which occurs not infrequently. Dyspepsia of an intermittent type, often loosely described as "cholecystic," may occur in the absence of any lesion except in the pancreas. One must assume that it is produced by a disturbance of the function of neighboring organs, which is not specific. The syndrome of surgical shock which occurs in some of the cases of pancreatic necrosis is probably produced mainly through the presence of autolyzed tissue in the retroperitoneal space, and partly by reflex disturbances mediated through the numerous nerves in this region. Extravasation of blood may add a small element to the total.

The syndrome of chronic pancreatic insufficiency, which is rare, is characterized by increased loss of fat, nitrogen and, probably, carbohydrate in the stools. Thus fatty diarrhea, with its nonspecific sequelae, is found. Malnutrition and weakness are invariable manifestations, while combinations of macrocytic anaemia, glossitis, hypotension, pigmentation of the skin, clubbing of the fingers, hypoproteinemia, vitamin D deficiency, vitamin K deficiency and disturbances in electrolyte metabolism are possible. While the steatorrhoea of complete pancreatic deficiency is more severe than that of idiopathic types, the incidence of these complications is less frequent. Nonetheless, they may occur, and differentiation of the two types may be difficult. Excess of nitrogen in the stools—normally, less than 3 gm. excreted per day—suggests a pancreatic deficiency, but high levels are found in late stages of severe idiopathic steatorrhea. The fat in the stools of patients suffering from pancreatic disease should be unsplit but, in some cases, the action of intestinal lipases and possibly bacteria causes it to be split. Unless the clinical history is very clear, proof that the pancreas is at fault may depend on finding that pancreatic enzymes are absent from the duodenal juice. The stools may appear fatty on gross inspection or on microscopic examination with fat stains. However, these methods will not always suffice. Recent experience shows that the best criterion of excessive fat loss is the demonstration that the total daily excretion of fat exceeds 10 per cent of the dietary fat intake. Also it is unsafe to conclude that the presence of recognizable striated muscle fibers in the stool means that excess nitrogen is being excreted, although it is suggestive evidence.

The serum amylase test appears to be of value, but with certain reservations. It must be remembered that the amylase is not a single

enzyme but a group of enzymes which have overlapping fields of action. Various methods of estimation have been evolved, by which one may measure the disappearance of substrate (starch), the production of intermediate products (erythrodextrin) or of end products (maltose). These methods give results which are not in close agreement and the results have been expressed in arbitrary units of differing value which makes comparison difficult. Fortunately the deviations which have clinical importance are quite gross so that the chemical defects of the test are less significant. The possibility of technical error must also be kept in mind since the determination may not be done frequently in smaller centers with the result that aberrations may occur in both the technician and the reagents. These difficulties can be overcome if one is aware of them; they do not appear to have been sufficiently emphasized. The serum lipase test is subject to even greater errors.

The clinical situations in which serum amylase determinations are useful are those in which acute damage to the pancreas has been produced. Under such circumstances the enzyme levels rise quite sharply within a few hours, and fall again to normal in twenty-four to forty-eight hours. This means that the test must be done early in the course of the disease if it is to be helpful, and that serial estimations are of more value than single ones. An elevated value does not distinguish between primary and secondary involvement of the pancreas so that the result must be interpreted with careful reference to the whole clinical picture. A normal value does not exclude acute pancreatic disease. In chronic diseases the serum amylase is usually normal, while some workers report that the serum lipase may be high.

Acute Pancreatitis.—This disease ought to be described as acute pancreatic necrosis and the mild form, which is called acute pancreatic edema or interstitial pancreatitis, probably differs only in degree. They will be discussed with reference to an analysis of thirty-three cases taken from the records of the Toronto General Hospital in the past

TABLE 1

ACUTE PANCREATITIS: INCIDENCE IN THIRTY-THREE CASES

Sex:	Males, 15; females, 18.						
Age:	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	70 to 80	(Decade)
	4	3	8	5	8	5	(Cases)
Obesity:	Obese, 11; not obese, 13; not described, 9.						

five years. Clinical data are lacking in some of these charts, either because the patient was in a private ward or because he was too ill to give the desired information. However, such cases were retained in the group if the pathological findings, laboratory work or other factors

made them of interest and convinced one of the diagnosis. The details regarding certain features are presented in tabular form, and reference will be made here to those characteristics which seem especially interesting.

With regard to incidence, it will be noted that the age spread is wider than commonly believed, that obesity which is often described

TABLE 2

ACUTE PANCREATITIS: SUBJECTIVE FINDINGS IN THIRTY-THREE CASES

Onset: Sudden, 22 cases; gradual, 6 cases; no record, 5 cases. Sudden onset of mild pain with gradual or sudden increment in 10 cases.

Pain:

Location

Epigastrium	16 cases	Left upper quadrant	2 cases
Umbilical region	5 "	Right upper quadrant	3 "
Both hypochondria	6 "	Generalized	3 "

Character		*Radiation*	
Crampy	9 "	Midback	13 "
Severe	7 "	Shoulder blades	3 "
Sharp	6 "	Flanks	3 "
Gnawing	2 "	Tips of shoulders	1 "
Dull	1 "	Left breast	1 "
Burning	1 "	No radiation	4 "
		Not described	5 "

Persistence

Steady	12 cases
Remittent or undulating	12 "
No record	9 "

Vomiting: Present in 20 cases; absent in 6; no record in 7.

Bowel Function:

Normal	16 cases	
Constipation	6 "	(habitual in 2)
Loose stool	2 "	
Diarrhea	1 "	
Flatulence	2 "	
No record	6 "	

as a predisposing factor was absent in a good proportion, and that the sex distribution was impartial. Alcohol was mentioned as a factor in only one case.

The subjective characteristics of the attacks are variable, as shown in Table 2. While the onset is usually sudden, it may be gradual. The pain is predominantly midline or bilateral in this series, and usually radiates to the middle of the back, but great variations are possible. The pain may be agonizing and steady, but a surprising number of the patients described their pain as remittent or undulating in severity.

The character of the pain was also variously described and, while it was most frequently described as crampy, one is not sure what the patient meant by that term. It usually persisted for several days, which may help to distinguish it from some of the biliary diseases. Inquiry into the past health of these patients revealed that a surprising number seem to have had attacks of a similar nature before, and that others had had chronic indigestion of a type commonly attributed to gallbladder disease, although some of them were later demonstrated to have a normal gallbladder.

TABLE 3

ACUTE PANCREATITIS: PAST HEALTH IN THIRTY-THREE CASES

	No. of cases	
Dyspepsia—chronic or recurrent (postprandial flatulence or pain)	11	
Absent	6	
No specific note	16	
Attacks of Severe Pain	9	
Absent	7	
Probably absent	17	
Cholecystectomy Previously	3	
Duodenal Ulcer	1	
Gallbladder Lesions	21	
Anatomical:		
Normal	4	(history of dyspepsia in 3)
Thick-walled, with stones	9	
Thick-walled, with "mud"	1	
Distended, with gravel	1	
Previously removed	2	
Radiological:		
Negative gallbladder series	4	

Similar variations, on a lesser scale, were seen in the presenting picture on examination. Thus, the syndrome of shock which is traditionally associated with this illness was absent twice as frequently as it was present. The complete picture of peritoneal irritation was not found but suggestive signs, such as rebound tenderness and mild hypertonicity of the abdominal muscles, were frequent. The location of the point of maximum tenderness was extremely variable. On the other hand, while vomiting and distention were very common findings, normal bowel function persisted in a striking number of cases.

The laboratory findings also varied somewhat. Although the white count was nearly always elevated, it was normal in six cases. The finding of albumin, with or without red cells and white cells, in the

urine was common and glycosuria was rare. The serum chlorides were low in those cases in which the determination was made. The non-protein nitrogen was elevated less constantly. A minority of patients showed some elevation of the van den Bergh. The serum amylase was usually elevated in the first day of the disease and for a variable time

TABLE 4

ACUTE PANCREATITIS: PHYSICAL FINDINGS IN THIRTY-THREE CASES

	No. of Cases
Shock or Cyanosis:	
Absent	18
Present	8
Perspiring but normal blood pressure	3
No record	4
Distention:	
Marked	14
Slight	4
Epigastric	1
Absent	7
No record	7
Peritoneal Irritation:	
Localized muscle splinting—	
Present	9
Absent	16
No data	8
Rebound tenderness—	
Present	4
Absent	12
No specific note	17
Location of Tenderness (absent in 2 and slight in 3 cases):	
Diffuse	11
Epigastrium	10
Umbilical region	3
Both upper quadrants	4
Both loins	1
Right upper quadrant	5
Right lower quadrant	1
Right upper and lower quadrants	1
Left upper quadrant	2
Left loin	1

afterward. Recent workers have noted a lowering of the calcium, protein and prothrombin content of the blood during acute attacks. The practical value of these findings remains to be determined. X-ray studies gave no specific help, and frequently suggested a diagnosis of intestinal obstruction.

TABLE 5

ACUTE PANCREATITIS LABORATORY AND X RAY FINDINGS IN THIRTY THREE CASES

	No. of Cases
Urinalysis	
Albumin—Present	17
Absent	10
Sugar— Present	4
Persistent	1
Red and white blood cells commonly present in small numbers.	
White Blood Count	
Normal	6
Elevated (range to 30,000)	27
Chlorides, Nonprotein Nitrogen, van den Bergh	
Occasionally disturbed	

Serum Amylase in 16 Cases

Hospital Days—	1	2	3	4	5	6	7	8	9	10
	−	−	−	+	+					
	+	−	−	+	−	−	−	0	−	0
	+									
	+	−	−	0						
	−	−	0							
	+	+								
	+									
	+	0								
	+									
	+	−	−	0						
	+									
	0									
	−	−	−	−	−	−	−	−	0	
	+	−	0							
	+	+								
	−	+								

+ = elevated
0 = normal
− = not done

X-ray Flat plate of abdomen (15 cases)	
Dilated loops of small bowel	6
Single dilated loop	1
Dilatation of the stomach	1
Dilatation of the colon	2
Calcification in upper abdomen	2
Negative	4
Gastric Series, during convalescence (3 cases)	
Negative	3
Positive	0
Gallbladder Series, during convalescence	4
All negative	

TABLE 6

ACUTE PANCREATITIS: ANALYSIS OF THIRTEEN DEATHS IN A SERIES OF THIRTY-THREE CASES

	No. of Cases
Complications:	
Palpable mass	4
Jaundice	3
Duodenal obstruction	2
Diabetes mellitus	1
General peritonitis	1
Cyst	1
Abscess	1
Thrombosis of veins (portal and mesenteric)	1
Mortality:	
Nonoperative therapy (23 cases) (percentage—35)	9
Operation, early or late (10 cases) (percentage—40)	4

TABLE 7

ACUTE PANCREATITIS: ANALYSIS OF THIRTEEN DEATHS IN A SERIES OF THIRTY-THREE CASES

	No. of Cases	Deaths
Age:		
Over 70 years	5	4
60 to 70 years	8	4
40 to 60 years	13	5
Under 40 years	7	0
Previous Similar Attacks:		
Present	9	6
Absent	7	4
No record	17	3
Preceding Dyspepsia:		
Present	11	6
Absent	6	2
No record	16	5
Apparent Cause of Death:		
Circulatory collapse—immediate		1
delayed		1
Duodenal obstruction		1
Infection—abscess		1
peritonitis		1
Diabetic coma		1
Liver damage		1
Widespread necrotic changes		1

The state of the gallbladder was noted in seventeen cases, either at operation or autopsy, and it was most frequently found to be diseased. It is possible that this group, representing as it does some of the most seriously ill patients, may not be an accurate indication of the whole. It is interesting that of the four patients whose gallbladder was seen to be normal, three had had previous attacks of dyspepsia, one of them with jaundice. Four patients who were not operated upon were found to have normal cholecystograms after their attack of pancreatitis had subsided.

The complications which may mar the clinical course are fairly mirrored in this series. It should be noted that in this center, as in most others, these patients are not operated upon if the diagnosis is made with certainty, but certain late complications must be watched for as an indication for surgical measures. Patients who were operated upon initially were closed without drainage or interference with the bilary tree unless there was an indication for doing one of these things. Cholecystectomy was performed at a later date in one or two patients who presented evidence of gallbladder disease, and others were requested to return for investigation of the biliary tree. Most of these failed to do so. Medical measures included the use of continuous gastric suction, intravenous administration of saline and glucose and, occasionally, transfusions of blood or plasma, with sedation as required. The mortality remains high in spite of these measures and consideration of the autopsy reports suggests that there was little hope of recovery from the outset in many of the cases.

When one comes to examine the records of those who died, one is impressed by the effect of age, preceding attacks of pain and preceding dyspepsia in determining the severity of the illness. In several cases there was fibrosis of the intact parts of the pancreas, tending to confirm the belief that previous attacks of pancreatitis had occurred.

Most of these patients appear to have had necrosis of the pancreas, although it is difficult to distinguish the condition from edema. This is usually differentiated on the basis of milder signs and symptoms with a more benign course, but many patients seem to fall into an intermediate zone and the correlation between the severity of the lesion and the clinical picture presented by the patient is not close. Wider use of the serum amylase test in patients with obscure upper abdominal pain has undoubtedly increased the frequency with which the diagnosis has been made in milder cases.

The facts brought out in this series agree in the main with similar studies on a larger scale which have been made elsewhere. The most striking finding seems to be the variability of the clinical picture, indicating that undue adherence to a classical concept of the disease will lead to mistakes in diagnosis.

Chronic and Recurrent Pancreatitis.—There is a group of patients who may be seen repeatedly with what appear to be attacks

of acute pancreatitis. This condition, which may be termed recurrent pancreatitis, is characterized by the development of a chronic lesion of increasing severity. It is not a rare disease: a recent report from the Mayo Clinic has indicated that eighty-nine such patients were seen there in a period of five years, while in our own center records of more than twenty have been gathered (Dr. W. K. Welsh, personal communication). The attacks which occur are indistinguishable from acute pancreatitis. The patient may be well in the intervals between attacks or may complain of chronic dyspepsia. Diabetes as a transient complication following the attacks has been seen, eventually becoming permanent in occasional cases. On the other hand, it may be absent though the pancreas appears to have been almost completely destroyed. Cystic changes of greater or less degree almost always occur and calcification of the pancreas is said to represent a frequent end stage of the condition. The syndrome of pancreatic insufficiency may be seen at a late stage when the acinar tissue has all been destroyed. Interference with the bile duct and duodenum may occur and, less frequently, with the veins related to the pancreas. It is obvious that the damage which is done occurs during the acute exacerbations, so treatment is aimed at preventing these. The diet should be low in fat, with small meals and avoidance of alcohol. If evidence of disease of the biliary tract is found, corrective surgical procedures should be carried out though it must be noted that this does not always arrest progression of the pancreatic disease. Resection of portions of the pancreas has been carried out occasionally in patients with severe pain in whom the process was more or less confined to one part of the gland.

Chronic fibrosis of the pancreas may also develop insidiously, producing few distinctive symptoms, often in patients with chronic gallbladder disease. It is discovered incidentally at operation. Usually one cannot determine whether it has developed as a result of repeated mild attacks of pancreatitis or by a steadily progressive process. It may have accounted for an unidentified proportion of the dyspepsia which was attributed to the biliary disease. Occasionally a patient may have pain of the pancreatic type and, in some cases, the syndrome of pancreatic insufficiency develops.

Pancreatic lithiasis is an accompaniment of chronic pancreatitis which scarcely merits separate discussion. In some cases the stone is large and single and its removal may benefit the patient. In others multiple lithiasis occurs, often associated with diffuse calcification of the gland parenchyma. In either case the clinical picture is one of chronic dyspepsia, often associated with acute episodes of pancreatic edema or necrosis. While it is evident that the presence of a stone will increase the likelihood of progressive fibrosis of the pancreas, it is not certain that the stone represents the primary point in the cycle.

There is some evidence to suggest that lithiasis is a fairly late complication of the pancreatitis.

Congenital Fibrocystic Disease.—Pancreatic insufficiency may appear in infancy in a pathological setting which resembles chronic pancreatitis but which proves to be more complicated on closer study. It appears to have a congenital, and even a familial incidence. The syndrome begins at birth either with the onset of meconium ileus or with the immediate appearance of fatty stools. The infant may soon die as a result of malnutrition. If not, he develops repeated pulmonary infections with fibrosis, bronchiectasis and patchy atelectasis of the lung. In these cases the disease proves fatal before the teens are reached. It has been suggested that milder forms may go unrecognized until adult life, but there is no proof of this.

On examination of the pancreas, one finds that the acinar tissue has disappeared, with replacement by fibrous tissue or by fat. The ducts are tortuous and show cystic dilatations although gross obstruction is not found to account for them. Changes in the epithelium and glandular structures in other organs suggest that the pancreatic lesion is part of a widespread disturbance. Thus the pulmonary infections are determined by a change in the bronchial epithelium from ciliated columnar to squamous, with an increase in the viscosity of the secretions. This does not appear to be attributable to vitamin A deficiency. The pancreatic lesion may be due to obstruction of minute ducts by an altered secretion with secondary changes following.

The condition may be difficult to distinguish from celiac disease but the fact that it begins earlier in life and is invariably accompaned by pulmonary lesions usually serves to differentiate it. Proof of the matter may be obtained by examination of the pancreatic juice.

Treatment of this condition is based on the same principles as that of pancreatic insufficiency in adult life, although it differs in detail. Since unabsorbed fat contributes to the diarrhea, the fat content of the diet should be reduced. However, an effort should be made to give as large a ration as possible. The protein allotment should be high in order to allow a positive nitrogen balance which is even more important in childhood than in adult life. The use of hydrolyzed protein by mouth, as a supplement, would be indicated if it were not so unpalatable and so expensive. Andersen has suggested that protein should make up 25 per cent of the total caloric intake. Digestion of carbohydrate is impaired least of all, so it can be allowed to make up the remainder of the diet but a good deal of it should be in the form of sugar. Vitamins A and D should be provided in large amounts and the possibility that vitamin K deficiency may develop should be kept in mind. The use of liver extract or folic acid is indicated to forestall a deficiency in these factors. Preparations of pancreatic enzymes in concentrated form are available. They are dispensed in enteric-coated

tablets to protect them from destruction in the stomach, which makes them difficult to use in the treatment of infants. Raw pancreas has also been used as a source of enzymes although it is difficult to disguise.

The recurrent pulmonary infections are frequently staphylococcal and should be treated by early administration of penicillin.

In spite of all these measures, the disease has always been fatal at an early age. In adult forms of pancreatic insufficiency, a considerable reduction of the disability may be achieved.

Pancreatic Cysts.—True cysts of the pancreas are rare, although several varieties are described. They may be neoplastic or due to retention, and have no distinctive clinical characteristics. The commonest cystic lesion is a collection of fluid which develops following acute pancreatic necrosis. This may involve the whole of the lesser sac with closure of the foramen of Winslow, or it may occupy a cavity on the surface of the pancreas which is lined with fibrous tissue. Because there is no epithelial lining, this is spoken of as a pseudocyst. Its fluid usually contains altered blood and pancreatic enzymes. It may become large enough to cause serious disturbances in the function of neighboring organs. It may discharge its contents into the gastrointestinal tract or peritoneal cavity, disappearing in a rather disconcerting fashion.

The accompanying symptoms are variable. The patient is sometimes aware of a mass in his abdomen but has little discomfort. On the other hand, the syndrome of boring pain, dyspepsia, weight loss and disturbances of gastrointestinal function, which accompanies so many of the pancreatic diseases, may be present. On examination, a swelling which is usually obviously cystic can be felt. It does not move freely with respiration as a rule and may bear a variable relationship to the liver, stomach, transverse colon and mesentery. Its origin in the retroperitoneal tissues is usually evident, while x-ray studies of the gastrointestinal tract frequently show evidence of displacement or compression by a smooth-walled tumor.

The treatment is surgical, consisting usually of evacuation and marsupialization of the cyst. Excision of cysts is attended by a higher mortality, and frequently followed by the formation of an external fistula. Production of a permanent fistula into some portion of the gastrointestinal tract may predispose to subsequent infection of the cyst, although the validity of this objection may be open to question.

Pancreatic Fistula.—From the medical point of view this complication of pancreatic surgery is of interest because of the metabolic changes which ensue. The severity of these changes will depend in part upon the proportion of the total pancreatic secretion which is being lost. If the pancreatic juice is almost entirely diverted to the exterior, a most complicated picture may be found because of the added effects of impaired digestion and absorption of food. Pancreatic

juice is alkaline and contains a fairly high concentration of calcium and chloride ion. Thus a marked disturbance of electrolytes may occur which, in turn, leads to impairment of renal function with nitrogen retention. These disturbances may be counteracted by returning the fluid drained from the fistula to the gastrointestinal tract by way of a duodenal tube, but parenteral fluids and salt are usually needed. Measures which have already been mentioned may be used to reduce the activity of the pancreas, with the addition of atropine or ephedrine. If the amount of drainage can be reduced in this way, the fistula may gradually close. Surgical therapy tends to be disappointing and should not be undertaken until the fistula has been given every opportunity to close spontaneously.

Anatomical Abnormalities.—These are rare, and seldom diagnosed if present. The ones which are of clinical significance are heterotopia of pancreatic tissue and annular pancreas encircling the duodenum. Heterotopic deposits may occur almost anywhere in the gastrointestinal tract, and may lead to ulceration, hemorrhage, perforation or partial obstruction. Obscure symptoms may be produced by such lesions in the pyloric region. The symptoms of an annular pancreas are due to obstruction of the duodenum. They may occur in infancy or be delayed till old age.

Benign Tumors.—Insulin-secreting tumors may be diagnosed through the disturbance in glucose metabolism which they produce. Other types of benign tumor may occur but they are of no clinical significance.

Carcinoma of the Pancreas.—Carcinoma may arise from the acini, the ducts or, rarely, the islet tissue. These lesions make up from 1 to 4 per cent of all carcinomas. No significant etiological factors can be identified. The symptoms which are produced are largely determined by anatomical factors. Diagnosis of the condition is difficult and usually made late in the disease. Even at operation the surgeon may not be certain whether carcinoma is present or not, and unfortunately the problem cannot be resolved by taking a biopsy. These difficulties must be overcome if present-day advances in radical surgery are to be successfully applied.

Study of the symptomatology and findings in forty cases proven at autopsy or diagnosed at operation in this hospital revealed considerable variations. Painless jaundice occurred in ten cases, the tumor being very small and possibly arising from the ducts or ampulla in six of these. Pain was a striking symptom in twenty-five cases; jaundice in twenty-two. These symptoms appeared simultaneously in three cases in a setting which suggested that a gallstone was present but the correct diagnosis was established at operation. In a fourth case, the history was similar but the passage of time had clarified the situation. Pain was the earlier symptom in nine cases, preceding jaundice by more than a month in all but three. Pain without jaundice was found

in thirteen cases. Three patients had neither pain nor jaundice. Jaundice preceded pain only once. In all cases weakness and weight loss had made an insidious appearance long before the patient came to hospital. Symptoms of duodenal obstruction developed at an early stage in five patients, with invasion of the duodenum and stomach contributing to the later symptoms in four others. Gastrointestinal hemorrhage had been seen in ten patients but its significance is doubtful because this series is drawn from the period before vitamin K was in use. Analysis of more recent cases has not yet been carried out. Two patients had severe diabetes.

Enlargement of the liver, usually but not always due to secondaries, was noted at examination in twenty-four cases. The gallbladder was palpably enlarged in twelve and demonstrated to be enlarged at operation or autopsy in seven additional cases. The spleen was palpable in three cases, a mass in twelve, and there was ascites in three cases.

X-ray examination of the upper gastrointestinal tract was carried out in sixteen of these patients, and gave significant information in eight. The changes noted were widening of the duodenal loop, displacement of the stomach and duodenum, and obstruction of the duodenum. These findings appear to be late and inconstant.

The tumor had apparently arisen in the head of the pancreas in twenty-five cases, in the body and tail in nine, and possibly from the ampulla or bile duct in six. In most of these last cases, the opinion is based on findings at operation and so are not quite conclusive. It should be remembered that there is an inherent error in such a series as this since it represents a degree of selection. Many of the cases of painless jaundice were diagnosed as carcinoma and the patients were sent home without operation, with the result that they do not appear either in the operative or autopsy series.

It will be seen that, while painless jaundice is a highly significant finding, it is not by any means invariable. However, the onset of jaundice in patients with preceding pain was uneventful and not accompanied by any increase in pain or colic, so that its nature was usually quite clear. The nature of the pain was also quite different from that usually encountered in biliary colic, being steady and relentless, gnawing and often radiating to the back. Occasionally periodic exacerbations of pain occurred, which were difficult to account for. It tended to be aggravated when the patient lay down at night and, as noted before, had a tendency to involve a wider area than that found with smooth muscle colic.

The syndrome which results from obstruction of the duodenum is often surprisingly obscure since a pronounced biochemical disturbance occurs which tends to mask the picture. Chloride depletion, alkalosis, nitrogen retention, dehydration and possibly tetany may be accompanied by a peculiar state of somnolence and lethargy, with behavior

which might be interpreted as psychotic or hysterical. Pigmentation of the skin may occur in company with marked malnutrition. The patient may not appear to be vomiting as much as he is, and radiological studies may not reveal the obstruction. It is a good principle to assume that a disturbance of the serum chlorides and alkali reserve in a vomiting patient is produced by interference with gastric outflow until conclusive evidence on the point has been obtained.

While the clinical findings associated with carcinoma of the body and tail of the pancreas are not presented separately, our data are in accord with those presented by Duff. The tumor tends to become much more widely disseminated, either because the patient lives longer after its inception or because of anatomical factors such as the peritoneal investment, the wider lymph drainage and the facility of spread by way of the splenic vein. Jaundice may occur, usually later, due to compression of the hepatic ducts by secondaries. Thrombosis of the splenic vein may lead to splenomegaly, while ascites may result either from obstruction of the portal vein or implantation of carcinoma on the peritoneum. Pain is an early symptom.

Curative therapy does not yet appear to be within reach although advances are being made in the field of radical surgery. It has been urged that palliative procedures should be carried out not only for the relief that they may give but also to give an opportunity of exploration. It is suggested that one may thus make sure that there is not a carcinoma of the bile duct, a localized lesion at the ampulla, a silent stone, or even chronic pancreatitis. Actually these hopes are so seldom realized that they do not constitute an argument. Palliative operations for the relief of jaundice do not bring relief from pain, so that the patient's lot may still be an unhappy one. In patients whose illness begins with painless jaundice and in whom itching becomes intolerable, a short-circuiting operation should be considered. It will usually put an end to itching at once, with subsidence of the jaundice at a rate depending on its duration and severity before operation. While the patient's appetite improves and he gains weight, the general symptoms of malignant disease soon become manifest. The majority of patients who survive the operation are dead in six months, and few live longer than a year.

Investigation of means whereby an earlier diagnosis can be made has been stimulated by the prospect that curative measures may some day be available. Extensive studies of the enzyme content of the duodenal juice after secretin injections have been made, following the technic mentioned earlier. Changes in the volume of juice, its bicarbonate content and each of its enzymes must be looked for, since in some cases only one of these components was altered. The results are difficult to interpret and considerable experience is necessary before the test can be properly assessed. It has also been suggested that analysis of the feces for fat and nitrogen may give useful information.

Physical Examination: The patient was a well developed, poorly nourished, acutely ill, white male. He was somewhat confused mentally. The skin was dry, and he was moderately jaundiced. There was evidence of recent weight loss. There was a purulent postnasal drip, and some papilledema. The breath was foul, and the cervical lymph nodes were enlarged and discrete. The lung fields were hyperresonant, and the heart was deviated to the left. There was flaring of the inferior costal margins. Liver dullness began in the 4th interspace on the right. Voice and breath sounds were normal and there were no rales. The point of maximal impulse was in the 4th interspace, 13 cm. from the midsternal line, and it was weak and diffuse. The rhythm was regular and no murmurs were heard. Blood pressure was 124/80. The abdomen was dome-shaped and the skin over the abdomen was tense. The paraumbilical veins were prominent. There was shifting dullness in the flanks and a fluid wave could be elicited. The liver extended 7 to 8 cm. below the costal margin, and the border was irregular. Hemorrhoids were present, and there was slight clubbing of the fingers.

Laboratory Data: The urine was clear, yellow and acid with a specific gravity of 1.018. On one occasion 2 plus protein was reported, but no proteinuria was found on another examination. No glucose was present. There were 3 to 5 red blood cells and 8 to 12 white blood cells per high power field. Hemoglobin was 9 gm. on admission with 4,130,000 red blood cells per cu.mm. There were 17,250 leukocytes per cu.mm., with 77 per cent neutrophils, 17 per cent lymphocytes and 6 per cent monocytes. On March 11, 1947, the urea nitrogen was 9.5 mg.; two days later it was 51.7 mg. per 100 cc. The icteric index was 22. The direct van den Bergh was negative and the indirect, 1.4 units. The total protein was 5.8 gm. with 1.5 gm. of albumin and 4.3 gm. of globulin. The Mazzini test was negative. Prothrombin time was 100 per cent of normal; the cephalin flocculation test was 4 plus at twenty-four hours. An x-ray of the chest was reported as "heart shadow indistinct. Both diaphragms elevated. A small platelike area of atelectasis is noted just above the right diaphragm. These changes are probably due to abdominal distention." Paracentesis fluid was reported as: "In a slight amount of fibrin there are packed red blood cells and some white blood cells. No neoplastic cells are discernible."

Clinical Course: An abdominal paracentesis was performed, and approximately 600 cc. of dark bloody fluid was removed. Additional fluid was not removed because of the sanguineous character. The temperature rose to 101°–102° F. daily. The pulse rate varied between 100 and 120 and the respiratory rate between 12 and 36. Infusions of whole blood and plasma were given in addition to infusions of crystalloids. The patient also received sedation, ferrous sulfate, choline chloride and crude liver extract. Upon surgical consultation it was felt that an operation was not indicated. On March 13, 1947, it was noted that the patient had almost complete urinary suppression. An indwelling catheter was inserted. The course was rapidly down-hill, and the patient expired on March 17, 1947, the seventh hospital day.

CLINICAL ANALYSIS

DR. MCCLURE: Although there are many indefinite points in the history, we are fortunate in at least two respects: (1) we can be reasonably sure that this man was in good health in 1934 and, (2) the signs and symptoms which first announced the present illness, i.e., gastric hemorrhage, were so dramatic that there can be little question as to their true nature. Profuse hematemesis of "fresh blood" must be an effect of severe hemorrhage in the stomach or esophagus. With only this information one would consider first the possibility of massive hemorrhage from a peptic ulcer. Against this is the lack of

characteristic ulcer symptoms, e.g., the hunger-pain, food-relief syndrome. We should like very much to know something of the two weeks period of hospitalization and study following this first hematemesis, but apparently such information is not available. We do not know with certainty whether the patient then vomited blood at intervals of several months, or experienced a quiescent period of a year or so, but the important thing is that massive hematemesis recurred. The hemorrhage must have been severe because the patient lost consciousness. Following an attack of this sort, and about five months before death, it is recorded that the abdomen became swollen and this was later diagnosed as ascites. This immediately leads us to consider portal hypertension as a cause of the repeated hematemesis. The onset of jaundice two months later (three months before death) markedly strengthens our view that some chronic hepatic disease is the primary basis for all of these signs and symptoms. This is further reinforced by the physical findings reported at the time of hospitalization. Blood pressure was normal and there is no mention of increased systemic venous pressure either from direct measurement or as reflected by distended veins of the neck, so that we may presume this important evidence of heart failure to be lacking. It is said, however, that the point of maximal impulse was weak, diffuse and 13 cm. from the midsternal line. One might consider this as evidence of cardiac dilatation and thus congestive failure, but there is a good possibility that this reflects simply an accumulation of serous fluid in the pericardial cavity. The hepatic enlargement plus the dilatation of paraumbilical and hemorrhoidal veins are excellent supportive evidence for chronic hepatic disease and indicates that ascites was a result of portal hypertension. Laboratory data provides some help, but there are some findings which are difficult to reconcile with our present view. For instance, the normal prothrombin time hardly seems compatible with the strongly positive cephalin flocculation test and with our clinical evidence of hepatic disease. The low plasma proteins and reversed albumin-globulin ratio is additional indirect evidence of hepatic dysfunction and helps also to explain the patient's edema. I would have expected a lower red cell count in this patient on the basis of past hemorrhages.

What hepatic disease would best explain this picture? We must consider two major types: one, that this is an effect of neoplastic involvement; two, that this represents cirrhosis. If this were a case of neoplastic involvement, where is the primary site of origin? The liver itself is unlikely since primary neoplasms are quite uncommon there and those that do occur are most apt to arise in bile ducts and to produce jaundice rather than portal hypertension as an outstanding initial sign. Those neoplasms which most commonly metastasize to the liver arise in the gastrointestinal tract or pancreas since hematogenous tumor emboli arising from these organs must enter the

portal vein and encounter the mechanical filter imposed by the hepatic capillary bed. We have no evidence to suggest a malignant neoplasm in any of these sites and it is extremely improbable that such a primary neoplasm would remain silent from one to two and a half years after metastatic involvement in the liver became clinically evident. When we think of silent or hidden primary sites of malignant neoplasia we must always think of lung and prostate, but these two seem unlikely because of the long interval of time and because neither characteristically gives extensive and bulky metastasis to the liver. The aspiration of dark bloody fluid from the peritoneal cavity suggests that hemorrhage into the peritoneal cavity was related to the terminal event. It may be that this came about from rupture of a markedly dilated vein which was serving to conduct blood from the portal vein directly to the vena cava. On the other hand the presence of bloody fluid in any large serous cavity suggests malignant neoplasia. The urinary suppression which characterized the last few days of life might have been an expression of marked ascites with sufficient pressure to interfere with renal circulation, hemorrhagic shock, terminal cardiac failure with hypotension, or perhaps dehydration.

In summary, I believe it most likely that this patient had Laennec's (portal) cirrhosis with resulting portal hypertension, and that the portal hypertension was the basis for the repeated hematemesis and for hemorrhage into the peritoneal cavity terminally. Of almost equal likelihood, I would consider that this patient had a malignant neoplasm of the liver, probably metastatic in origin. One point in favor of this latter hypothesis is the fact that the liver was large, firm and irregular. Ordinarily in cirrhosis, at this rather late stage, the liver is shrunken and atrophic. The presence of bloody ascitic fluid also suggests carcinoma.

CLINICAL DISCUSSION

QUESTION: Is it usual for nutritional edema to localize in the lower legs and feet?

DR. MCCLURE: Characteristically, the edema of hypoproteinemia is often pronounced in the large serous cavities, but actually there is edema of all tissue and this is under the influence of gravity. If this is associated with sodium chloride retention or even a slight degree of cardiac failure, the combination of effects may produce considerable dependent edema.

QUESTION: How do you reconcile the normal prothrombin time with the apparent hepatic deficiency?

DR. MCCLURE: Hepatic function tests are notoriously poor guides as to the exact state of liver function since but one tenth or so of a normal liver is sufficient to carry out proper function. Then, too, there is evidence that, varying from case to case, some functions may be lost before others. There is possibility, too, that the report is in error.

PATHOLOGIC FINDINGS (Dr Hopps)

Gross.—External examination at necropsy revealed an extensive area of subcutaneous hemorrhage, ecchymosis, centering about the abdominal paracentesis wound and measuring 62 by 24 cm. The appearance suggested that slow oozing of blood had continued for several days and up to the time of death. In addition there were multiple petechiae over the trunk. Certainly this reflected a bleeding tendency on the part of this patient and would belie the report of 100 per cent prothrombin time.

The *peritoneal cavity* contained approximately 4000 cc of dark red fluid, the consistency of thin cream. Several small blood clots were in

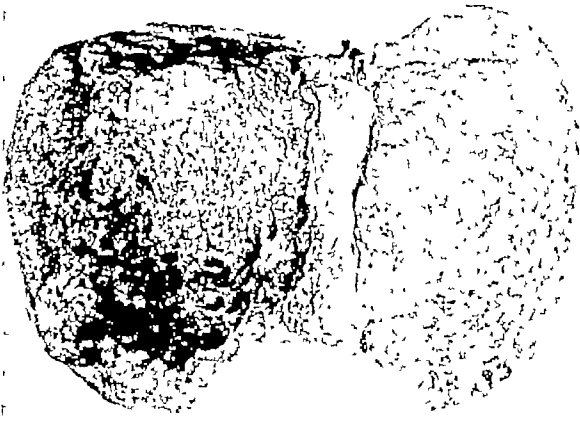

Fig. 101.—Liver, diaphragmatic surface. These multiple nodules were soft and cream-colored in contrast to the usual finding in the Laennec's cirrhosis

cluded. The specific gravity of this fluid was 1 015, the hematocrit reading (erythrocytes) was 10.5 per cent—no hemolysis was evident. Thus of the 4 liters of peritoneal fluid, approximately 1 liter represented blood.

The *liver* extended 7 cm. below the inferior costal margin in the right midclavicular line and its surface was composed almost entirely of rather soft, creamy-white, hemispherical nodules averaging 1 cm in diameter. Over the anterior margin of the right lobe a mass of indurated omentum was tightly adherent. This mass, 4 cm. in diameter, was infiltrated with blo.. ..d appeared to be the site of intraperitoneal hemorrhage. The actual source of bleeding was the liver itself, an ulcerated necrotic nodule immediately underlying the

adherent omentum. The liver weighed 2075 gm., an increase of about 600 gm. over normal. Cut surfaces revealed that approximately 90 per cent of the liver was composed of soft cream-colored nodules similar to those observed on the external surface. The color and consistency of these were in striking contrast to the usual picture in Laennec's cirrhosis. There was considerable increase in fibrous tissue within the remaining parenchyma and surrounding the nodules just described, so that cirrhosis did exist in addition to what appeared to be a primary malignant neoplasm.

Further examination disclosed a small lymph node at the porta hepatis which was replaced by tumor tissue. The portal vein appeared

Fig. 102.—Liver, inferior surface. Observe in the lower left portion of the figure a conglomerate mass of tumor nodules which has undergone ulceration.

essentially normal save for moderate dilatation, but the hepatic vein contained a tumor thrombus which almost completely filled the lumen of this vessel (see Fig. 103). Extrahepatic bile ducts were moderately dilated and patent. The gallbladder contained, in addition to approximately 100 cc. of dark green viscid bile, four faceted pigment stones averaging 1 cm. in diameter.

The *spleen* was very firm, enlarged about five times (720 gm.) and adherent by fibrous adhesions to the posterior abdominal wall. External and cut surfaces presented changes characteristic of chronic passive congestion. This together with patchy areas of markedly dilated venous channels beneath the parietal peritoneum of the lower abdomen and large (collapsed) varicosities in the lower one third of the esophagus was positive evidence that portal hypertension had

existed. Other abdominal viscera were not remarkable save for the *kidneys*. These exhibited icteric nephrosis characterized by greenish-brown discoloration, a swollen, glazed appearance and considerable increase in weight (195 and 220 gm.).

The right *pleural cavity* was almost completely obliterated by dense fibrous adhesions; the left did not present adhesions nor did it contain appreciable fluid. Both leaves of the diaphragm were elevated, lying at the level of the third rib. This was largely an effect of the hepatic enlargement with ascites, and was reflected by considerable basilar

Fig. 103.—Porta hepatis. Observe the tumor thrombus which fills and projects from the hepatic vein.

atelectasis. In addition there was slight to moderate bronchiectasis in both lungs, and both lungs exhibited edema and lumpy consolidation posteriorly, a manifestation of hypostatic bronchopneumonia. The heart was not remarkable save for slight atrophy. At the time of death there was but 30 cc. of serous fluid present in the pericardial cavity.

Microscopic.—Histopathologic studies did not alter our provisional anatomic diagnosis, but did reveal interesting changes in the liver. The picture was similar in the ten sections studied. The multilobular portal cirrhosis was striking and these broad bands of fibrous tissue contained relatively few inflammatory cells. The great majority of hepatic tissue was neoplastic as evidenced by anaplasia, pleomorphism, disorderly arrangement and a tendency toward destructive invasion of

surrounding tissues. Invasive characteristics were best demonstrated in the portion of omentum which was adherent to the liver. Of the remaining non-neoplastic hepatic parenchyma, there were complete lobules (up to .3 cm.) and large portions of other nodules which had undergone fairly recent (days) coagulation type necrosis. I believe that this is one of the most significant findings relating to the immediate cause of death in this patient. As the tumor thrombus grew, within the hepatic vein, it reached a point, probably but a few days before death, of almost complete obstruction. This so markedly decreased venous circulation as to bring about multiple foci of infarction within the liver and acute hepatic failure, reflected by the areas of recent coagulation necrosis. It seems reasonable to suppose also that this may have been a major factor in the intraperitoneal hemorrhage. So far as the terminal period of anuria is concerned, this is quite characteristic of the hepatorenal syndrome. It is my opinion that the hepatorenal syndrome is most often intimately related to the marked parenchymatous degeneration which the kidney suffers as a consequence of jaundice, i.e., icteric nephrosis. Certainly this condition markedly interferes with renal function, so that what might ordinarily be a trivial injury, when superimposed upon an already existing diffuse toxic damage, precipitates renal failure.

Our final anatomic diagnosis is:

Hepatic cirrhosis, portal, with primary carcinoma, hepatic cell type
Esophageal varicosities, ascites, and chronic passive congestion of the spleen, with recent hemorrhage into the peritoneal cavity
Jaundice with icteric nephrosis, marked
Thrombosis of the left major hepatic veins (tumor thrombus)
Hypostatic bronchopneumonia, bilateral, with chronic bronchiectasis, slight
Basilar atelectasis of lungs with compensatory emphysema
Extensive pleural fibrous adhesions, bilateral
Apical pulmonary tuberculosis, inactive, bilateral
Cholelithiasis (pigment stones)
Cystitis, acute
Atrophy of right testicle
Hyperplasia of bone marrow
Accessory spleen

DISCUSSION

QUESTION: What do you consider the relationship between the cirrhosis and the carcinoma?

DR. HOPPS: The majority of primary carcinomas, hepatic cell type, occur in connection with portal cirrhosis. It is likely that this relationship exists because both conditions are an effect of what, in the broad sense, we might term chronic irritation. The nutritional status

also certainly has a great deal to do with portal cirrhosis and recent data indicates that it may also play a major role in the genesis of carcinoma of the liver. The occurrence of primary carcinoma of the liver is highest in certain peoples of Africa. It has been demonstrated experimentally and confirmed by clinical observation that in these natives, as a result of their peculiar diet deficient in certain of the B vitamins and having also an imbalance of amino acids, degenerative changes occur in the liver. These, if continued, lead to cirrhosis and this probably explains the predisposition to and very high incidence of primary hepatic cell carcinoma in these people.

CUMULATIVE INDEX